

Bulletin No. 50 from the Department of Surgery,

University of Lund, S-221 85 LUND

1985

MANAGEMENT OF THE OCCLUDED ILIAC VEIN



Gunnar Plate



From the Department of Surgery, University of Lund,

S-221 85 Lund, Sweden

**MANAGEMENT OF
THE OCCLUDED ILIAC VEIN**

by

Gunnar Plate

Lund 1985

To my dear father

The present thesis is based upon the following papers, referred to in the text by their Roman numerals.

I Thrombectomy with temporary arteriovenous fistula. The treatment of choice in acute iliofemoral venous thrombosis.

Gunnar Plate, Eibert Einarsson, Per Ohlin, Ragnar Jensen, Peter Qvarfordt and Bo Eklöf.

J Vasc Surg 1:867-76, 1984.

II Pulmonary embolism in acute iliofemoral venous thrombosis.

Gunnar Plate, Per Ohlin and Bo Eklöf.

Submitted to Br J Surg.

III Iliac vein obstruction associated with acute iliofemoral venous thrombosis: Results of early reconstruction using polytetrafluoroethylene grafts.

Gunnar Plate, Eibert Einarsson, Bo Eklöf, Ragnar Jensen and Per Ohlin.

Submitted to Acta Chir Scand.

IV Overcoming failure of venous vascular prostheses.

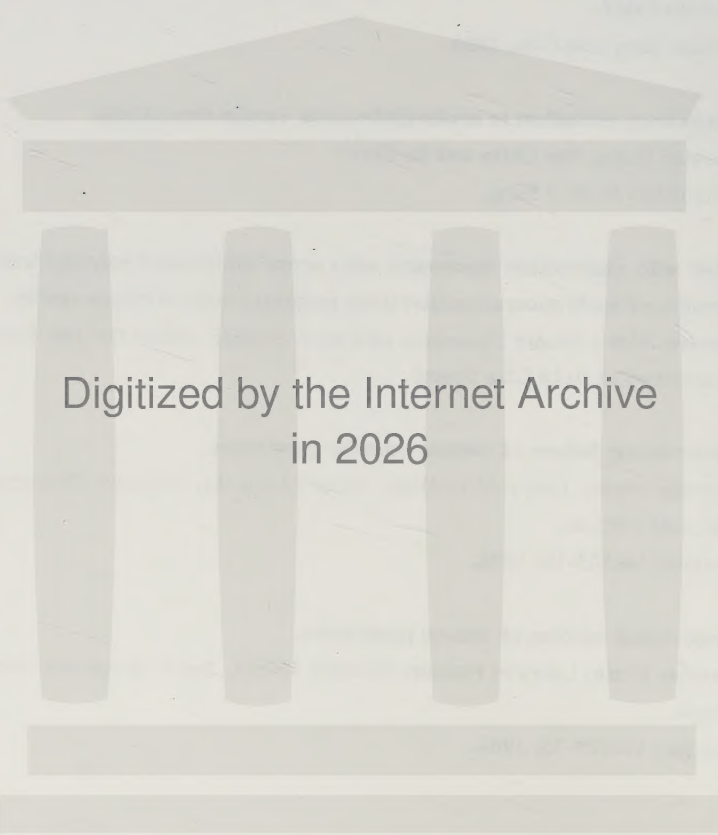
Gunnar Plate, Larry H Hollier, Peter Gloviczki, Mrinal K Dewanjee and Michael P Kaye.

Surgery 96:503-10, 1984.

V Endothelial seeding of venous prostheses.

Gunnar Plate, Larry H Hollier, Richard J Fowl, Jon R Sande and Michael P Kaye.

Surgery 96:929-36, 1984.



Digitized by the Internet Archive
in 2026

https://archive.org/details/IA41552414_0086

CONTENTS

	<u>Page</u>
Introduction.....	7
Aims of the present investigation.....	14
Materials and methods.....	15
Results.....	18
General discussion.....	22
Management of acute iliofemoral venous thrombosis.....	22
Anticoagulation.....	22
Thrombolysis.....	24
Thrombectomy.....	26
Avoidance of pulmonary embolism.....	27
Preservation of iliofemoral patency.....	30
Preservation of femoropopliteal valvular competence.....	32
Management of acute iliofemoral venous thrombosis with associated chronic iliac vein obstruction.....	34
Management of chronic iliac vein obstruction.....	36
Direct reconstruction.....	36
By-pass reconstruction.....	37
Experimental development.....	38
Venous prostheses.....	38
Manipulation of graft characteristics.....	38
Endothelial seeding.....	39
Systemic antiaggregation.....	41
Arteriovenous fistula.....	41
Support of graft wall.....	42
Conclusions.....	44
Future prospects.....	46
Acknowledgements.....	48
References.....	49

INTRODUCTION

"Chronic ulceration of the lower extremity following deep venous thrombosis is a condition that undoubtedly has plagued the human race since man assumed the erect position" (Linton, 1953). Postthrombotic sequelae including limb edema, venous ulcers and leg pain during exercise (venous claudication) not only cause personal suffering but also have significant economic implications for both the individual and society. After a population survey comprising 13,160 individuals Gjörës (1956) calculated that the prevalence of individuals with a history of deep venous thrombosis was around 2 %. Of these, 94 % had chronic symptoms, 12 % had a reduced income and 3 % had lost the ability to work.

Acute iliofemoral venous thrombosis

An iliofemoral venous thrombosis involves the common and external iliac veins but often affects the entire deep venous system of the lower extremity (Dodd & Cockett, 1967). In such cases, the risk of complications like pulmonary embolism, venous gangrene and postthrombotic sequelae is imminent (Fontaine & Tuchmann, 1964; Mavor & Galloway, 1969). Without treatment, the incidences of fatal embolism and limb loss have been around 18 % and 4 %, respectively (Bauer, 1946; Haller & Abrams, 1963; Havig, 1977). Höjensgård (1952) recorded persistent limb edema in 80 %, venous ulcers in 28 % and leg pain in 42 % of 89 patients following thrombosis affecting the entire extremity.

Anticoagulation therapy with heparin and vitamin K antagonists, which was introduced in the 1940's entailed that both fatal embolism and venous gangrene could be avoided in most patients with deep venous thrombosis (Bauer, 1946). At most institutions, anticoagulation is still the only treatment used for deep venous thrombosis. However, long-term observations have revealed that postthrombotic sequelae develop in 36 - 90 % of patients with iliofemoral thrombosis treated with anticoagulants alone (Fontaine & Tuchmann, 1964; Denck, 1977; O'Donnell et al., 1977; Elliot et al., 1979; Browse et al., 1980).

During the latest decades, thrombolytic agents like streptokinase or urokinase have been employed in the treatment of deep venous thrombosis. Some authors

imply that such treatment is more effective than anticoagulation for prevention of pulmonary embolism (Kaçkar et al., 1969; Widmer et al., 1974; Elliot et al., 1979), but others have noted that embolism is more frequent during thrombolysis (Denck, 1977; Arnesen et al., 1978). Thrombolytic treatment seems less effective for extensive thrombi (Mavor et al., 1973; Widmer et al., 1974; Common et al., 1976; Baker, 1977; Kriessmann et al., 1977; Arnesen et al., 1978; Gmelin & Theiss, 1978) and postthrombotic sequelae have been reported in 25 - 70 % following iliofemoral thrombosis (Mavor et al., 1973; Johansson et al., 1976; Denck, 1977; Elliot et al., 1979, Albrechtsson et al., 1981a). Adverse treatment effects, like severe bleeding and "spontaneous" rupture of parenchymatous organs, have deterred many physicians from using thrombolytic therapy (Eklöf et al., 1977).

Surgical thrombectomy of deep venous thrombosis was occasionally attempted during the first decades of this century (Schnitzler, 1911; Leriche, 1927; Låwen, 1937), but larger series were not reported until the late 50^s and early 60^s by Mahorner et al. (1957), Haller & Abrams (1963), Bradham & Buxton (1964), DeWeese (1964) and Fontaine & Tuchmann (1964). They claimed that this procedure not only prevented fatal pulmonary embolism and venous gangrene but also was effective in avoiding the late postthrombotic sequelae. These reports were succeeded by several enthusiastic series demonstrating excellent early clinical results following thrombectomy (Hafner et al., 1965; Kaiser et al., 1965; Smith, 1965; Britt, 1966; Little et al., 1966; Palma, 1968). When Lansing & Davis in 1968 presented a long-term follow-up of Haller & Abrams' series demonstrating that late sequelae and valvular incompetence had developed in the majority of the patients, the enthusiasm for thrombectomy was turned into scepticism and abandonment. In addition, the risk of creating pulmonary embolism during thrombectomy has probably deterred many physicians from surgical interventions. Karp & Wylie (1966), Mavor & Galloway (1969) and others (Brunner & Wirth, 1971; Johansson et al., 1973) have showed that rethrombosis following thrombectomy is extremely common and is responsible for the postoperative embolism as well as the late postthrombotic sequelae.

At some institutions, attempts at refining the surgical technique to avoid embolism and rethrombosis have continued. Fogarty introduced the balloon catheter which makes venous thrombectomy easier, more effective and perhaps

safer (Fogarty et al., 1966; Brunner & Wirth, 1971). Alemany & Helmig (1977) and Kistner & Sparkuhl (1979) advocated that thrombectomy should be combined with permanent vein interruption to avoid postoperative embolism. Egeblad et al. (1970) and Mansfield et al. (1971) stressed the importance of intraoperative phlebography to ensure completeness of vein clearance. For the same purpose Kiely (1973) suggested exploration of the veins below the knee. Others (Bertelsen, 1969; Mavor & Galloway, 1969; Edwards et al., 1970; Lindhagen et al., 1978; Provan & Rumble, 1979; Goto et al., 1980) have used infusion of heparin or thrombolytic agents directly into the thrombectomized vein to reduce the incidence of early rethrombosis. Some recent reports of iliofemoral thrombectomy using variations of these new techniques have been encouraging (Lindhagen et al., 1978; Horsch et al., 1979; Kistner & Sparkuhl, 1979; Nedjbat et al., 1979; Provan & Rumble, 1979; Goto et al., 1980; Andriopoulos et al., 1982), but the long-term results are not well elucidated.

Kunlin (1953) and Bryant et al. (1958) have demonstrated that a flow-increasing arteriovenous fistula is effective in preventing thrombosis of vascular transplants in the venous system. Such a fistula, therefore, has been adopted as a means of preventing rethrombosis following thrombectomy (Maillard & Gillot, 1970; Köpf & Stahlknecht, 1973; Brunner, 1974). A few larger series of thrombectomy combined with a temporary arteriovenous fistula have yielded promising early results (Poilleux et al., 1975; Hutschenreiter et al., 1979; Delin et al., 1982). This method was used in 70 patients with acute iliofemoral thrombosis admitted to the Department of Surgery, University of Lund, Sweden from 1974 - 1979. Preliminary reports have demonstrated few sequelae in nearly all patients and preserved iliac vein patency in two thirds of the patients at 6-month follow-up (Einarsson et al., 1981).

Before therapeutic routines are changed, the new methods need to be tested against conventional treatment (e.g. anticoagulation). The great variation in reported incidences of pulmonary embolism and postthrombotic sequelae following medically as well as surgically treated iliofemoral venous thrombosis is most likely due to differences in patient selection, techniques, follow-up time and to subjectivity in evaluation of patients' complaints. Therefore, establishment of therapeutic routines on the basis of retrospective uncontrolled clinical studies is

inappropriate. Prospective, controlled and preferably randomized studies using objective criteria in the follow-up are required to define the optimal therapy. Such studies including phlebographic follow-up and preferably functional evaluation of venous drainage and reflux, comparing thrombectomy with anticoagulation have been repeatedly requested (Eriksson et al., 1967; Barner et al., 1969; Kakkar et al., 1969; Baumann, 1976; Elliot et al., 1979; Horsch et al., 1979), but have never been performed before.

Acute iliofemoral venous thrombosis with associated chronic iliac vein obstruction

Several etiologies of chronic iliac vein obstruction are known (May & DeWeese, 1979), but the most common cause is a compression of the most cranial segment of the left common iliac vein between the overriding iliac artery and the spine (May & Thurner, 1965; Cockett et al., 1967). This "iliac compression syndrome" causes turbulence of the blood flow, intimal damage and formation of intraluminal fibrous strands and membranes (vein spurs). Although present in around 20 % of all adults (May & Thurner, 1956) the iliac compression syndrome usually is asymptomatic unless secondary iliofemoral thrombosis develops (Cockett et al., 1967; May & DeWeese 1979; Partsch, 1981). In these situations, attempted thrombectomy is even more frequently followed by postoperative rethrombosis and late sequelae (Cockett & Lea Thomas, 1965; Mavor & Galloway, 1969; Vollmar et al., 1978; Welter & Becker, 1981).

Surgical reconstruction of iliac vein obstructions has been attempted in the late postthrombotic stage, but this is often impaired by fibrosis and valvular incompetence of the femoropopliteal veins (May & DeWeese, 1979). Reconstruction of the associated chronic obstruction in conjunction with acute thrombectomy could theoretically be more successful, but this has been described in only a few case reports (Cockett & Lea Thomas, 1965; Wagner et al., 1973; Gaylis, 1974; Johnsson et al., 1974; McNeill & Sorour, 1980), and the long-term results of such a combined procedure are not known.

Chronic iliac vein obstruction

Reconstruction of chronic iliac vein obstructions has been performed with either a direct repair or a by-pass procedure (May & DeWeese, 1979). Direct reconstructions are accomplished by decompression and/or disobliteration of the obstructed vein (Eufinger et al., 1961; Cockett & Lea Thomas, 1965; Johnsson et al., 1974; Vollmar, 1978), the long-term benefit of which remains to be proven (May & DeWeese, 1979; Welter & Becker, 1981). By-pass reconstructions became popular after Palma & Esperon (1960) presented a small group of patients operated upon with a cross-femoral by-pass utilizing the contralateral long saphenous vein (Palma procedure). Larger series of the Palma procedure have been presented by Husni (1971) and Dale (1979) demonstrating satisfactory clinical results but long-term reports have been insufficient, especially concerning late phlebographic follow-up. Dumanian et al. (1968), Vollmar & Laubach (1970), Frileux et al. (1972) and Krug et al. (1974) recorded several early graft occlusions following the Palma procedure which prompted them to add a flow-increasing arteriovenous fistula. The need for such a fistula has been disputed by others (Dale, 1979; May, 1981).

Autogenous vein has been the preferred graft material for venous reconstruction (Husni, 1971; Dale, 1979; Kunlin & Kunlin, 1979). However, the long saphenous vein sometimes is inadequate in size for drainage of the entire lower extremity (Dumanian et al., 1968), and following iliofemoral thromboses these veins are frequently destroyed (Vollmar et al., 1978; Gruss et al., 1981). In these situations, synthetic graft materials are required. A limited clinical experience using expanded polytetrafluoroethylene grafts for iliac vein reconstruction has been encouraging (Gruss et al., 1979; Hutschenreiter et al., 1979), but long-term results still are missing.

Since iliac vein reconstruction is not established among clinical routines, it is of major importance that the results are documented objectively. Clinical criteria occasionally are deceptive when determining graft patency (Dale, 1979). Evaluation of late patency rates following venous reconstruction, therefore must include follow-up phlebograms (Dale, 1979; Kistner & Sparkuhl, 1979; May & DeWeese, 1979). In addition, measurement of femoral venous pressures at rest and during exercise provides important information on the functional status of the

iliofemoral segment (Negus & Cockett, 1976; Albrechtsson et al., 1981b; Weber, 1981). Reports of venous reconstructions missing these ingredients in the follow-up, therefore should be regarded with scepticism.

Experimental development

Experimental development of vascular prostheses suitable for the venous system has been going on for several decades (Dale & Scott, 1963; Haimovici et al., 1970; Scherck et al., 1974; Hiratzka & Wright, 1978; Kunlin & Kunlin, 1979). All vascular prostheses are more or less thrombogenic (Sawyer et al., 1978; Kunlin & Kunlin, 1979), and no ideal substitute has been found. Hitherto, the most promising early results have been achieved with the expanded polytetrafluoroethylene graft (Soyer et al., 1972; Fujiwara et al., 1974; Smith et al., 1975; Fiore et al., 1982). Systemic administration and incorporation into the graft material of antiaggregatory agents (anticoagulants, antiplatelet drugs etc) have been attempted to decrease the deposition of thrombotic material on the internal graft surface, but without obvious impact on the long-term patency rates (Haimovici et al., 1970; Hiratzka & Wright, 1978; Gloviczki et al., 1984). Endothelial seeding has recently been introduced as a means of decreasing graft thrombogenicity in the arterial system (Herring et al., 1978; Graham et al., 1979; Sharefkin et al., 1982). The clinical experience with endothelial seeding is minimal (Herring et al., 1984a) and this method has not been attempted previously in the venous system. The low blood flow velocity and low intraluminal pressure within the venous system are for the most part responsible for the disappointing results with venous vascular prostheses (Kunlin & Kunlin, 1979). Addition of a flow-increasing arteriovenous fistula and external support of the graft wall have been attempted to overcome these problems, but the value of these adjunctive procedures is still debated (Scherck et al., 1974; Hiratzka & Wright, 1978; Kunlin & Kunlin, 1979). Late graft occlusions have been accredited to strictures developing at the anastomoses of autogenous as well as synthetic vein grafts. External support of the anastomosis and a meticulous surgical technique have been proven to decrease this complication (Gottlob & May, 1977; Kunlin & Kunlin, 1979).

Vascular prostheses and adjunctive procedures for venous reconstruction have been evaluated mainly by patency studies following replacement of various vein

segments in experimental animals. Transformation of the recorded data to clinical practice is often compromised by insufficient observation times or implantation of too short graft segments (Dale & Scott, 1963; Hiratzka & Wright, 1978). Usually, the prostheses have been placed in the superior or inferior vena cava where the high blood flow velocity provides better graft patency than in the peripheral veins (Kunlin & Kunlin, 1979). Some confusion also has been created by postocclusive recanalization, which has been described following both autogenous and prosthetic reconstructions (Dale & Scott, 1963; Hiratzka et al., 1981). For the above mentioned reasons, experimental evaluation of vascular prostheses and adjunctive procedures for venous reconstruction should include serial long-term patency studies following implantation of prostheses of adequate length at the appropriate position in the venous system. The development of new techniques for evaluation of graft morphology (Sawyer et al., 1978; Ford, 1982) and of the in vivo deposition of platelets and fibrin on the graft surface (Dewanjee et al., 1981) have made it possible to determine the impact on the thrombogenicity of the graft-blood interface by various manipulations of graft characteristics and by drug administration.

AIMS OF THE PRESENT INVESTIGATION

- I To compare clinical results, iliofemoral venous patency and femoropopliteal valvular competence following thrombectomy combined with a temporary arteriovenous fistula and systemic anticoagulation to the results obtained with anticoagulation alone in the treatment of acute iliofemoral venous thrombosis.
- II To study the incidence of pulmonary embolism in acute iliofemoral venous thrombosis treated with anticoagulation alone and in combination with thrombectomy and arteriovenous fistula.
- III To study the long-term results of polytetrafluoroethylene prostheses used for reconstruction of a chronic iliac vein obstruction and implanted early after an associated acute iliofemoral venous thrombosis.
- IV To study, in a relevant experimental model, the value of various techniques (e.g. manipulation of graft characteristics, arteriovenous fistula and external ring-support) on decreasing thrombogenicity and improving patency of polytetrafluoroethylene grafts in the venous system and to compare these results to the results obtained with autogenous vein grafts.
- V To study the value of endothelial seeding on graft morphology and early patency of polytetrafluoroethylene vascular prostheses implanted in the venous system of dogs.

MATERIALS AND METHODS

These are here summarized and organized according to the original papers, which are referred to for a more detailed information.

I All patients admitted with swelling of the entire leg with a duration not exceeding 7 days underwent acute phlebography. Sixty-three patients with thrombi extending above the inguinal ligament but not into the vena cava were randomly allocated to conservative treatment with systemic anticoagulation (32 patients) or to acute thrombectomy combined with a temporary arteriovenous fistula and anticoagulation (31 patients). Five patients with incomplete initial phlebograms subsequently were excluded after it was found that the thrombus did not extend above the inguinal ligament. The thrombi affected the entire deep venous system of the involved limb in all but 5 patients. The two treatment groups were compatible concerning age and sex of the patients and site and duration of the thrombus (I: Table I).

Follow-up after six months included bilateral ascending and descending contrast phlebography with measurement of femoral venous pressures and doppler evaluation of venous reflux at the popliteal level. Development of early postthrombotic sequelae, preservation of iliofemoral venous patency and of femoropopliteal patency and valvular competence were compared for the two treatment groups.

II The same patient population was used as in study I. Presence of symptoms suggestive of pulmonary embolism was recorded. Objective evaluation of embolism at admission was performed with perfusion lung scanning in conjunction with chest radiography in 49 patients. The lung scans were classified as normal (no perfusion defects), inconclusive (atypical defects or defects corresponding to radiographic findings) or positive for embolism (lobar or segmental perfusion defects without corresponding radiographic findings). Improvement or development of additional emboli during anti-

coagulation treatment with or without thrombectomy and arteriovenous fistula was evaluated with repeated lung scanning at one week and one month.

- III Seven patients admitted for acute iliofemoral venous thrombosis with associated chronic iliac vein obstruction were subjected to thrombectomy and early venous reconstruction using polytetrafluoroethylene (PTFE) grafts. The reconstructions were performed in the same seance (four cases), after two days (two cases) or after 49 days (one case) and consisted of cross-femoral (four cases) or iliocaval (three cases) by-pass procedures using 8-10 mm non-ringed PTFE grafts supported by a temporary arteriovenous fistula (6 cases), anticoagulation (6 cases) and antiplatelet agents (1 case).

Graft patency was evaluated in the early postoperative course, at fistula closure after 3 - 6 months, at clinical deterioration and at 2-year follow-up using contrast and radionuclide phlebography. Physiological evaluation included venous plethysmography, foot volumetry and measurement of ambulatory foot vein pressures.

IV Part I

In eighteen dogs the inferior vena cava was resected and replaced with 5 cm segments of 10 mm ringed PTFE grafts. The thrombogenicity of ten control grafts and eight grafts wetted with heparin as described by Takamatsu (1982) was evaluated by 3-hour studies of patency and deposition of ¹¹¹In labeled platelets and ¹²⁵I labeled fibrinogen on the graft surface.

Part II

Following ligation of the left hypogastric and common iliac veins 44 dogs were subjected to iliocaval by-pass reconstructions with autogenous vein grafts or 8 mm PTFE grafts wetted with heparin as above. A side-to-side arteriovenous fistula was created at the femoral level in selected animals.

These fistulae were closed after one month. The dogs were divided into five groups (IV: Table I) for evaluation of graft material, arteriovenous fistula and external ring support upon graft patency. Phlebography was performed after one week and after one, three and six months. The animals were sacrificed if the graft had occluded, which abolished confusion by postthrombotic recanalization. All surviving dogs were sacrificed after six months, the graft patency was checked and the morphology was evaluated with light and electron microscopy.

- V Twenty dogs were subjected to ilio caval reconstruction as in study IV utilizing PTFE grafts supported by external rings and arteriovenous fistula in all cases. Ten grafts, pretreated with enzymatically derived and immediately seeded endothelial cells as described by Graham et al. (1982), were compared to 10 control grafts that were sham seeded with the same culture medium and autogenous blood. All grafts were harvested after 4 - 6 weeks, perfusion fixed in situ and examined with light microscopy, scanning and transmission electron microscopy for evaluation of endothelial coverage.

RESULTS

I The initial clinical course was satisfactory in both treatment groups. Leg swelling decreased rapidly and the patients were discharged after 9 (5-23) days in the conservative and after 11 (7-35) days in the surgical group. Early rethrombosis following thrombectomy occurred in three of 23 patients (13 %) examined with early postoperative phlebograms. All 3 patients had an associated iliac vein obstruction. In three other patients with associated obstructions, the caudal portion of the iliac vein remained patent following thrombectomy. One operated patient developed a compartment syndrome due to incomplete clearance of old thrombi in the peripheral veins which lead to gangrene and amputation of the leg above the knee. Minor wound complications developed in three (11 %) of the operated patients. One of the conservatively treated patients experienced recurrent pulmonary embolism requiring caval interruption.

Follow-up after six months was possible in 27 conservatively treated and in 24 operated patients, since six patients had expired from malignant disease and one patient had his leg amputated. Clinical examination (I: Fig 2) revealed that leg edema, new varicose veins and venous claudication were slightly more frequent (non-significant) in the conservative group and only 7 % of these patients were completely free from postthrombotic symptoms compared to 42% of the operated patients ($p < 0.005$).

Technically acceptable iliofemoral phlebograms were obtained in 26 conservatively treated and in 21 operated patients. The phlebographic status of the iliofemoral segments was significantly ($p < 0.025$) better in the surgical group than in the conservative group (I: Fig. 3). Simultaneous measurement of femoral venous pressure demonstrated a pressure increase that was significantly ($p < 0.001$) greater in patients with a fair or bad result compared to patients with an excellent iliofemoral segment. There was no significant ($0.05 < p < 0.1$) difference when comparing the pressure increase in the two treatment groups but measurements were missing in several anticoagulated patients with totally occluded veins.

Femoropopliteal phlebograms were obtained in 27 conservatively treated and in 23 operated patients (I: Fig 4). Around 1/3 of the patients of both groups had persistent occlusions of the superficial femoral or popliteal veins. In patients with open femoropopliteal veins the valves were also competent in 41 % of the patients in the conservative group and in 86 % of the patients in the surgical group ($p < 0.05$). Venous reflux recorded by doppler examination correlated well with phlebographic findings of valvular incompetence.

In all, nine patients had a completely open deep venous system with competent valves (I: Fig 5), normal femoral venous pressures, doppler studies without signs of reflux and no postthrombotic symptoms whatsoever. All these nine patients belonged to the surgical group. Of the six operated patients that had an associated chronic iliac vein obstruction, three remained asymptomatic whereas postthrombotic symptoms developed in the other three, in whom early rethrombosis had occurred.

- II At admission, 14 of the 58 patients (24 %) with acute iliofemoral venous thrombosis reported symptoms suggestive of pulmonary embolism. Lung scans obtained at admission in 49 patients were normal in 18 cases (37 %) inconclusive in 9 cases (18 %) and positive for embolism in 22 cases (45 %). There was a poor correlation between symptoms suggestive of embolism and positive scans (II: Fig. 1).

Additional perfusion defects after one week were slightly more frequent in the surgical than in the conservative group (non-significant), but the total incidence of new emboli within the first month was equal (around 20%) in both treatment groups (II: Table I). Most additional emboli were minor and asymptomatic but one conservatively treated patient required caval interruption. The perfusion defects disappeared or improved within one month in more than 80 % of the patients in both treatment groups.

- III Following thrombectomy and early reconstruction of associated chronic iliac vein obstructions, the clinical course was satisfactory in five patients but one patient died from postoperative complications and one patient's leg

was amputated after 20 months. At follow-up after two years only one graft was still patent, but this graft has remained patent for 5 ½ years. Neither clinical symptoms nor physiological parameters correlated to graft patency. All four patients that had an excellent clinical course despite graft occlusions still had a partial iliac vein patency with abundant collaterals.

IV Part I

Five of ten control PTFE grafts and one of eight heparin wetted PTFE grafts occluded within three hours after implantation in the canine inferior vena cava ($0.05 < p < 0.1$). The radionuclide studies revealed that the deposition of platelets and fibrin was greatest on the graft surface and at the cranial anastomosis (IV: Fig 2, 3). The heparin wetting procedure decreased platelet deposition at both these locations ($p < 0.01$, $p < 0.025$) whereas the decrease of fibrin deposition was not statistically significant.

Part II

The long-term patency of autogenous vein grafts implanted in the ilio caval position in dogs, was not influenced by use of an arteriovenous fistula (IV: Fig 4). No PTFE graft stayed patent without an arteriovenous fistula whereas 7 of 10 such grafts supported by a fistula were still patent after one month ($p < 0.05$). Only two of seven (29 %) fistula supported but non-ringed PTFE grafts were still patent after six months but this was not statistically different from the 60 % 6-month patency rate recorded with ringed PTFE grafts. By using the heparin wetting procedure, temporary arteriovenous fistula and external ring support the 6-month patency of PTFE grafts (60 %) was not significantly different from the results obtained with autogenous vein grafts (68 %). Morphologic studies of harvested grafts revealed that all autogenous vein grafts had a smooth endothelial lining without mural thrombi, whereas only one third of the patent PTFE grafts were free from thrombus and only 10 - 40 % of their mid-graft surface was covered by endothelium.

V Five endothelial seeded and seven sham seeded PTFE prostheses implanted in the ilio caval position in dogs remained patent until sacrifice after 4 - 6 weeks. Gross examination of the internal surface of patent grafts (V: Fig. 2) revealed an area free from thrombus of 80 ± 24 % following endothelial seeding and of 71 ± 26 % following sham seeding (non-significant). Light microscopy of thrombus-free areas in the graft center (V: Fig. 3) demonstrated a monolayer of cells resting on a basement membrane in all patent grafts. Scanning and transmission electron microscopy (V: Fig 4, 5) demonstrated that these cells exhibited most characteristics that are typical for endothelial cells (thin, flat, polygonal cells with interdigitating cell borders, tight junctions, pinocytotic vesicles, basement membrane and inconspicuous endoplasmic reticulum). No Weibel-Palade bodies were discovered in any graft of either group.

GENERAL DISCUSSION

Management of acute iliofemoral venous thrombosis

Three principally different modes of treatment are today available: anticoagulation, induced thrombolysis and surgical thrombectomy. The efficacy of these regimens will be scrutinized from the standpoint of their relative ability in preservation of venous patency and valvular function and in avoiding the major complications of venous gangrene, pulmonary embolism and late postthrombotic sequelae following iliofemoral thrombosis. The treatment of more peripherally located thrombi will not be discussed. Rheologic, antiplatelet and defibrinating agents have occasionally been used but they have not reached wide-spread acceptance in the treatment of acute deep venous thrombosis.

Anticoagulation

The purpose of anticoagulant therapy is to arrest thrombus build-up whereas already formed thrombi basically are unaffected. The individual's own fibrinolytic system could produce some lysis of the thrombus but restoration of venous patency mostly depends on late recanalization (Leu, 1968; Sevitt, 1978). Following iliofemoral thromboses recanalization is usually incomplete and available collateral pathways are limited (Cockett et al., 1967; Mavor & Galloway, 1967; Weber et al., 1973). No previous report has included clearcut data on late iliofemoral venous patency and valvular competence following acute iliofemoral venous thrombosis treated with anticoagulants alone. In our series only nine (35 %) of the anticoagulated patients regained an adequate venous outflow capacity as indicated by 6-month iliofemoral phlebograms and femoral venous pressures during exercise (I). No specific etiology, duration or site of the thrombosis characterized cases with an excellent iliofemoral result. The remaining 17 patients (65 %) developed residual stenoses or occlusions causing elevated femoral venous pressures during exercise, indicating a functional drainage incapacity.

Since the femoropopliteal veins generally are involved in the thrombotic process, valvular function in this segment is also jeopardized. Three quarters of our anticoagulated patients developed persistent femoropopliteal vein occlusions

(37 %) or valvular incompetence (37 %). Of the remaining 7 patients (26 %) that had a patent femoropopliteal segment with competent valves at follow-up, this segment had been only partly involved by the initial thrombosis in 3 cases. Thus, occasionally valvular competence is maintained following anticoagulation treatment alone.

Our study has demonstrated that, although around 70 % of the thrombosed veins are recanalized during anticoagulation, iliofemoral thromboses usually result in limbs with inadequate venous drainage and with venous reflux. Similar conclusions have been reached by others (Cockett et al., 1967; Weber et al., 1973; Watz & Savidge, 1979), although none of their studies were prospective and phlebographic follow-up was incomplete.

Early clinical improvement could be expected with anticoagulant treatment alone (I). Venous gangrene seldom develops except in cases with phlegmasia cerulea dolens (Bauer, 1946; Brockman & Vasko, 1965; Głowiczki et al., 1982). Pulmonary embolism has been controlled in most series of iliofemoral thrombosis (Bauer, 1946; Widmer et al., 1974; Denck, 1977; Watz & Savidge, 1979), but Fontaine & Tuchmann (1964) reported 11 % fatal emboli despite anticoagulation treatment. Details of their anticoagulation regimen were not provided and for this reason it could not be excluded that insufficient doses were administered. In our study adequate anticoagulation was ascertained by control of the activated partial thromboplastin time and by thrombotest. No fatal emboli occurred and only one anticoagulated patient required caval interruption (II). Routine lung scans detected minor emboli in around 20 % of the patients, but these did not require any additional measures. This demonstrates that adequate anticoagulation in most cases provides effective prevention against embolism.

The incidence of late sequelae following anticoagulation treatment of iliofemoral thrombosis has varied from 36 - 90 % (Fontaine & Tuchmann, 1964; Denck, 1977; Elliot et al., 1979; Browse et al., 1980). If the venous drainage remains severely impaired, leg swelling persists and calf pain during exercise (venous claudication) usually develops shortly after the initial thrombosis (Dodd & Cockett, 1976). Trophic skin changes like pigmentation, eczema and chronic ulceration are mainly due to peripheral disease and do not occur until several years later (Dodd &

Cockett, 1976). Kriessmann & Rupp (1977) noted a gradual deterioration of venous function starting about two years following iliofemoral thromboses. Therefore, the connection between the initial iliofemoral thrombosis and development of postthrombotic sequelae often is not appreciated. O'Donnell et al. (1977) reported severe incapacitating late sequelae in 18 of 21 patients at 10 or more years following anticoagulated acute iliofemoral venous thromboses leading to major limb amputations in 14 % of the patients. The validity of these data is uncertain since this series was retrospective and the patient selection was not quite clear. In our series, mild sequelae were present in 93 % of the patients at 6-month follow-up (1).

Thus, anticoagulant treatment provides satisfactory early clinical results, but late sequelae due to persistent venous occlusions and valvular incompetence are likely to develop within 5- 10 years. The lag time in the onset of postthrombotic symptoms explains why many physicians falsely consider anticoagulation treatment as effective for acute iliofemoral venous thrombosis.

Thrombolysis

Ideally, thrombolytic therapy provides a rapid dissolution of deep venous thrombi and pulmonary emboli with restoration of venous patency before the vein valves are destroyed and the lung has infarcted (Kakkar et al., 1969; Mavor et al., 1973; Widmer et al., 1974; Johansson et al., 1976; Kriessmann et al., 1977; Elliot et al., 1979). More extensive thromboses are less susceptible and lysis of iliofemoral thrombi has been reported in 19 - 85 % of the cases (Mavor et al., 1973; Widmer et al., 1974; Johansson et al., 1976; Baker, 1977; Kriessmann et al., 1977; Arnesen et al., 1978; Gmelin & Theiss, 1978; Elliot et al., 1979). In addition, restoration of venous patency often is incomplete and rethrombosis after discontinuation of therapy is common despite continued anticoagulation (Mavor et al., 1973; Stephens, 1976; Dhall et al., 1978). The great variation in reported patency rates could be due to differences in therapeutic routines. A communication by Theiss et al. (1983) indicates that better results are achieved if the thrombolysis is performed over a prolonged time.

Late phlebographic follow-up after thrombolysis is rarely reported, but ilio-femoral occlusions seem to persist in around half of the treated patients (Mavor et al., 1973; Johansson et al., 1976; Elliot et al., 1979). Albrechtsson et al. (1981a) recorded iliac vein occlusions in 38 % of 16 patients at 14 - 57 months following attempted thrombolysis, but the remaining patients had residual iliac stenoses with pathologically elevated femoral venous pressures. Valvular function of the femoropopliteal segment was preserved only in one patient in the whole series. Common et al. (1976), Johansson et al. (1976) and Elliot et al. (1979) noted that a normal valvular function was preserved in less than 50 % of patients treated with thrombolytic agents. Watz & Savidge (1979) were more successful in valve preservation but only a minority of their patients had iliofemoral thrombosis.

The initial clinical course is usually satisfactory with thrombolytic treatment (Widmer et al., 1974; Elliot et al., 1979). Venous gangrene has been avoided even in patients with phlegmasia cerulea dolens (Paquet et al., 1970; Norgren & Gjöres, 1977). Pulmonary embolism is routinely controlled (Widmer et al., 1974; Kriessmann et al., 1977; Elliot et al., 1979), although Denck (1977) and Arnesen et al. (1978) have experienced fatal emboli to be slightly more frequent with thrombolytic than with anticoagulant therapy. This is probably due to partial lysis and dislodgement of thrombotic segments. Evaluation of late sequelae following thrombolysis of acute iliofemoral venous thrombosis is compromised by too short follow-up and inclusion of patients with femoropopliteal thrombosis in most series (Kakkar et al., 1969; Widmer et al., 1974; Watz & Savidge, 1979; Albrechtsson et al., 1981a). In the reports by Johansson et al. (1976) and Elliot et al. (1979) only 30 - 42 % of the patients were asymptomatic at $\frac{1}{2}$ - 4 years following an iliofemoral thrombosis.

Severe hemorrhagic complications have been reported in 5 - 30 % of patients during thrombolysis (Duckert et al., 1975; Johansson et al., 1976; Kriessmann et al., 1977; Arnesen et al., 1978; Elliot et al., 1979). This precludes such treatment during pregnancy, in the puerperium and following trauma or surgery which are all situations where thrombosis commonly occurs (Barner et al., 1969; Edwards et al., 1970; Andriopoulos et al., 1982). Since thrombolysis is also contraindicated in patients with recent cerebrovascular accidents, hemorrhagic diathesis, severe hypertension, liver or kidney disease, gastroduodenal ulcers and in patients with

circulating antibodies against streptokinase, only around two thirds of all patients are amenable to thrombolytic treatment (Widmer et al., 1974; Watz & Savidge, 1979).

Thus, induced thrombolysis does not seem to provide early or late results that are clearly superior to the results achieved with anticoagulation alone. The great incidence of side-effects also makes this treatment less attractive for routine use.

Thrombectomy

In the early days, thrombectomy was accomplished by using forceps, suction catheter, external compression of the leg and by letting the patient perform Valsalva manoeuvre (Mahorner et al., 1956; Haller & Abrams, 1963; Bradham & Buxton, 1964). Since the balloon catheter technique was introduced by Fogarty in the early 1960^s a complete clearance of the iliofemoral segment is possible in nearly all patients with fresh thrombosis (Fogarty et al., 1966; Mavor & Galloway, 1969; Lindhagen et al., 1978). Notably, this device was not used in the crucial series by Lansing & Davis (1968) that demonstrated bad long-term results and caused abandonment of venous thrombectomy at most institutions in the United States. Hence, results obtained without the aid of Fogarty catheters will be disregarded in the following discussion.

Thrombi are amenable to surgical thrombectomy during the first 5 - 7 days (Wilson & Britt, 1967; Vollmar, 1978; Brunner, 1979). Ingrowth of fibroblasts and capillaries adheres the thrombus to the vein wall and precludes a complete vein clearance and preservation of valvular function at a later date (Dodd & Cockett, 1976; Sevitt, 1978; Brunner, 1979). Although, a complete clearance of the iliofemoral segment is possible in most early cases (Mavor & Galloway, 1969; Lindhagen et al., 1978), wall damage caused by the thrombus and by intravascular instrumentation commonly leads to postoperative rethrombosis despite simultaneous administration of anticoagulant drugs (Karp & Wylie, 1966; Brunner & Wirth, 1971). The reports by Brunner & Wirth (1971) and Johansson et al. (1973) demonstrated that iliac vein patency and valvular competence were both maintained in less than one third of the patients following thrombectomy. Kistner &

Sparkuhl (1979) reported significantly better results following 107 thrombectomies, but their series included several patients with thrombi confined to below the groin and the number of late phlebograms obtained was not stated. Most other reports demonstrating variable results are compromised by a significant heterogeneity in patient selection and treatment employed or by insufficient phlebographic follow-up (Fogarty et al., 1966; Barner et al., 1969; Kitainik & Quiros, 1972; Capdevila et al., 1975; Baumann, 1976; Matsubara et al., 1976; Alemany & Helmig, 1977; Denck, 1977; Horsch et al., 1979; Jocham & Abshagen, 1979; Nedjabat et al., 1979; Goto et al., 1980; Metz & Weber, 1980; Andriopoulos et al., 1982).

The early clinical results following thrombectomy are satisfactory. Urgent thrombectomy combined with systemic anticoagulation generally is effective in preventing limb loss in cases of phlegmasia cerulea dolens (Brockman & Vasko, 1965; Gloviczki et al., 1982). According to Fontaine & Tuchmann (1964), the incidence of fatal embolism in surgically treated patients is about one tenth that found in medically treated patients. Other series have been complicated by around 5% fatal emboli following thrombectomy (Mavor & Galloway, 1969; Kitainik & Quiros, 1972; Denck, 1977; Horsch et al., 1979). Development of late symptoms have varied considerably, but the most conclusive reports by Brunner & Wirth (1971) and Johansson et al. (1973) demonstrated late postthrombotic sequelae in 70 - 80% of the patients following thrombectomy.

Most authors agree that incomplete vein clearance and rethrombosis are responsible for postoperative embolism and late sequelae due to persistent iliofemoral occlusion and/or femoropopliteal valvular incompetence (Mavor & Galloway, 1969; Edwards et al., 1970; Brunner & Wirth, 1971; Johansson et al., 1973; Young et al., 1974; Stephens, 1976; Lindhagen et al., 1978; Kistner & Spahrkuhl, 1979). Therefore, additional measures are required to avoid these complications.

Avoidance of pulmonary embolism

To avoid intraoperative embolism Fogarty et al. (1966) and Brunner & Wirth (1971) have advocated temporary caval interruption by introduction of one or two protective balloon catheters via the contra- or ipsilateral groin veins placing the

inflated balloon in the infrarenal vena cava. Review of some larger series reveals that fatal intraoperative emboli have occurred in 1 - 4% of thrombectomies despite the use of "protective" balloons (Baumann, 1976; Denck, 1977; Horsch et al., 1979; Andriopoulos et al., 1982), and in 0 - 3% of cases operated upon without this extra device (Barner et al., 1969; Mavor & Galloway, 1969; Lindhagen et al., 1978; Goto et al., 1981; Röder et al., 1984). Thus, "protective" balloons do not seem to provide effective protection against pulmonary embolism. Consequently it is not warranted to risk damage to the healthy contralateral groin veins by introduction of balloon catheters from that side. It seems worthwhile, however, to use ipsilateral protective balloons in cases with hazardous ascending thromboses with a freely floating tail.

Kistner & Sparkuhl (1979) recommend routine ligation of the femoral vein in cases of ascending thrombosis, although in their series the incidence of postoperative embolism was not decreased with this procedure when compared to patients operated upon with thrombectomy alone. They claimed that vein ligation at the femoral level does not cause postthrombotic sequelae. Young et al., on the other hand, (1974) reported that postthrombotic sequelae were equally frequent in patients operated upon with thrombectomy and femoral vein ligation as in patients treated with anticoagulation alone. Little et al. (1966) and Alemany & Helmig (1977) found that fatal embolism was completely avoided by caval interruption performed prior to thrombectomy. They did not record late venous patency and postthrombotic sequelae, however. On the contrary, Edwards et al. (1970), Capdevila et al. (1975) and Hutschenreiter et al. (1979) have noted that postthrombotic sequelae occur more frequently if caval interruption is added to the thrombectomy. Thus, by adding a permanent vein interruption the main purpose of performing thrombectomy (to prevent postthrombotic sequelae) is eliminated and the incidence of pulmonary embolism is not clearly reduced.

Adequate preoperative phlebography (Nissl, 1979; Schmitt, 1981) seems of major importance in avoiding pulmonary embolism. Patients with thromboses extending into the vena cava are at great risk of developing severe embolism (Denck, 1977; Havig, 1977). Therefore, such cases must be detected preoperatively and should be operated upon with direct caval exploration or interruption prior to thrombectomy

(Fogarty et al., 1966; Brunner, 1979; Nedjbat et al., 1979). For caval interruption, the Greenfield filter technique seems preferable, since the incidence of caval thrombosis and postthrombotic sequelae is lower than with other methods (Greenfield et al., 1977).

Use of intraoperative fluoroscopy probably also helps in avoiding embolism. The proper position of the balloon catheter in the vena cava could be checked with fluoroscopy, thereby decreasing the risk of thrombus fragmentation during thrombectomy (Mansfield et al., 1971; Provan & Rumble, 1979). The completeness of vein clearance is assured with fluoroscopy, whereby the risk of rethrombosis and postoperative embolism decreases (Mavor & Galloway, 1969; Egeblad et al., 1970; Mansfield et al., 1971; Brunner, 1979).

Manipulation of the intracaval pressure during thrombectomy has been used to decrease the incidence of pulmonary embolism (Purtscheller, 1979). Positive-pressure ventilation and anti-Trendelenburg position provide a moderate but stable increase of intracaval pressures. Even higher pressures are achieved by letting the patient perform Valsalva manoeuvre (Spatenka et al., 1979), but this implies operation under local anesthesia. An adverse pressure gradient could develop, if the patient unexpectedly takes a deep breath whereby the risk for embolism increases (Purtscheller, 1979). The clinical value of elevated intracaval pressures has not been proven, and fatal emboli have occurred in 1 - 2 % of patients operated upon with either of the above techniques (Kitainik & Quiros, 1972; Denck, 1977; Horsch et al., 1979). If an embolus is dislodged during thrombectomy it seems unrealistic that an increased intracaval pressure could prevent rather than delay its further transportation towards the lung.

All our operations were performed under general anaesthesia using intraoperative fluoroscopy and a positive end-expiratory pressure but no "protective balloons" and all patients with caval thrombosis were excluded (I). Intra- and postoperative emboli were detected with serial lung scans in 21 % of the patients but these emboli were minor and did not occur more frequently than following anticoagulation treatment alone (II). By adhering to similar principles for avoidance of embolism others have also found thrombectomy to be a safe procedure (Dodd & Cockett, 1976; Lindhagen et al., 1978; Vollmar et al., 1978; Brunner, 1979; Provan

& Rumble, 1979; Metz & Weber, 1980). An adequate surgical approach guided by the preoperative phlebogram, a complete vein clearance checked by intraoperative fluoroscopy and avoidance of rethromboses are probably the most important factors in the prevention of pulmonary embolism.

Preservation of iliofemoral patency

A complete clearance of the iliofemoral segment is mandatory for preserved patency (Mavor & Galloway, 1969; Brunner, 1979). Residual thrombi must be detected. This is best performed by intraoperative radiography after contrast injection into the thrombectomized vein (Egeblad et al., 1970; Mansfield et al., 1971). Back-bleeding from the iliac vein, on the other hand, is an unreliable sign of vein clearance (Wilson & Britt, 1967; Edwards et al., 1970; Gaylis, 1974; Brunner, 1979).

With postoperative infusion of heparin directly into the thrombectomized iliofemoral segment via a retained intravenous catheter, the incidence of early rethrombosis of this segment has been decreased to 7 - 28% (Bertelsen, 1969; Mavor & Galloway, 1969; Lindhagen et al., 1978; Provan & Rumble, 1979). This catheter also allows control of early iliofemoral patency by repeated phlebography. Still, reocclusions occur following discontinuation of the regional heparin infusion and the late iliac patency rates have dropped to 49 - 63% (Mavor & Galloway, 1969; Lindhagen et al., 1978; Röder et al., 1984). Experimental studies by Einarsson et al. (1984) indicate that endothelial healing is not completed until 4 - 6 weeks following thrombectomy, but heparin infusion during this entire period is not practical. Yet, the early clinical course following thrombectomy with regional heparin infusion has been satisfactory and late sequelae have been recorded in 18 - 60% of the patients (Mavor & Galloway, 1969; Edwards et al., 1970; Lindhagen et al., 1978; Röder et al., 1984). This regimen could therefore be an acceptable alternative for patients with acute iliofemoral venous thrombosis.

Thrombectomy has also been combined with regional infusions of thrombolytic agents (Mavor et al., 1973; Matsubara et al., 1976; Goto et al., 1980). This combination seems advantageous but risky since haemorrhage is common during

thrombolysis and the surgical intervention creates a nidus for bleeding. Experience still is too limited to allow any definite conclusions regarding risks and benefits with this regimen.

A distal arteriovenous fistula allows prolonged protection against reocclusion following thrombectomy. The protective effect is mainly due to an increase in blood flow velocity (Dost, 1968; Kunlin & Kunlin, 1979). By utilizing an arteriovenous fistula the incidence of early rethrombosis of the iliofemoral segment has been decreased to less than 20 % (Poilleux et al., 1975; Hutschenreiter et al., 1979). In our series, only 13 % early rethrombosis were detected at routine phlebography on the first postoperative day. Early iliofemoral patency rates following this procedure have varied from 60 - 83 % (Vollmar et al., 1978; Einarsson et al., 1981; Delin et al., 1982). Our phlebographic follow-up demonstrated a completely normal iliofemoral segment in 76 % of the operated patients (I). These results were superior to the results obtained with anticoagulation treatment alone and better than most previously reported results with other regimens. The early clinical results have been excellent both in our series and others (Poilleux et al., 1975; Delin et al., 1982), but no data are available today on the incidence of late postthrombotic sequelae. Poilleux et al. (1975) reported postthrombotic symptoms in only 4% of the patients but the observation time was not stated. Future observations on our patients will hopefully provide more reliable information concerning the long-term results.

Some surgeons have used an arteriovenous fistula only in cases with old and incompletely removed thrombi and in cases with associated iliac vein obstructions (Senn & Althaus, 1973; Baumann, 1976; Denck, 1977; Horsch et al., 1979; Jocham & Abshagen, 1979; Gutschi, 1982). The results in these high-risk patients were often better than in patients with fresh thrombosis operated upon with thrombectomy alone (Baumann, 1976; Horsch et al., 1979).

Many surgeons have hesitated to use a fistula because of problems related to fistula closure. With refinement of the fistula technique the complications during closure could be abolished (Plate et al., 1981; Edwards, 1982). All our fistulae were closed in local anesthesia as an out-patient procedure and without complications (Plate et al., 1981).

Brunner (1979) has feared to use an arteriovenous fistula because of the risk for arterial damage. In some cases he has constructed a fistula by utilizing an arterial branch in the adductor canal. He did not describe how to close such a fistula, which might be more cumbersome than with our technique. We have not experienced any complications related to the arterial system and distal arterial pressures measured at 6-month follow-up demonstrated no difference when comparing the operated to the non-operated legs (unpublished data).

In conclusion, the most effective way to assure iliofemoral venous patency presently is by thrombectomy combined with a temporary arteriovenous fistula and systemic anticoagulation. This procedure also has proven safe and associated with few complications.

Preservation of femoropopliteal valvular competence

Clearance of the distal veins is accomplished by careful retrograde introduction of the balloon catheter from the groin. Competent valves often prohibit catheter passage but occasionally this problem is overcome by inflation of the balloon cranial to the valve. This procedure widens the vein which could permit further catheter passage (Brunner, 1979). With repeated attempts it is usually possible to pass the catheter 20 - 40 cm peripherally. Brunner (1979) advocates extensive exposure of the femoral veins and a long venotomy to allow clearance of all tributaries, but this increases the trauma to the femoral vein wall, creates a larger thrombogenic area and causes a risk for stricture following closure of the venotomy. In our experience, the femoral bifurcation could be sufficiently disobliterated through a transverse venotomy. Only one of our follow-up phlebograms demonstrated residual obstructions at this level.

In cases with fresh distal thrombi, effective clearance of the peripheral vein is accomplished by forceful manual compression of the leg from the foot towards the groin which extrudes residual thrombi through the venotomy. Wrapping with an Esmarch bandage has not proven more effective, which could be due to loss of the propulsive effect of arterial inflow. "Milking" of thrombi out of the deep veins has the advantage of avoiding endothelial damage, but the blood-loss could be excessive and pulmonary embolism must be prevented by temporary occlusion of

the cranial groin veins. Nachbur & Wiesmann (1977) have combined thrombectomy of the iliofemoral segment with regional perfusion of the affected limb with streptokinase utilizing extracorporeal circulation. The blood was drained from the femoral vein, filtered, and infused with streptokinase into the femoral artery. By this method, the effectiveness of thrombectomy and thrombolysis in clearing the veins is combined without risk of systemic side-effects by streptokinase. However, this regimen seems rather complicated and the risk of rethrombosis remains. Two of the six patients treated by Nachbur & Wiesmann reoccluded their veins in the early postoperative course. Yet the principle of optimizing peripheral thrombectomy by regional thrombolysis seems worth further testing.

Preservation of femoropopliteal patency and valvular competence also depends of course on continued iliofemoral vein patency. Therefore, an arteriovenous fistula placed in the groin, could be of importance in improving the femoropopliteal results as well. This is supported by our finding that femoropopliteal patency was preserved in 61 % and valvular competence in 52 % of the operated patients. The results are better than the results achieved with thrombectomy alone (Brunner & Wirth; 1971; Johansson et al., 1973), and most likely better than the results obtained with thrombolytic treatment (Johansson et al., 1976; Elliot et al., 1979; Albrechtsson et al., 1981a). Our study clearly demonstrated that preservation of valvular competence was more successful with our surgical procedure than with anticoagulation alone (I). Although restoration of femoropopliteal patency was equally frequent in both treatment groups, this was due to recanalization causing valvular destruction in the conservatively treated patients.

Occasionally, restoration of peripheral venous patency is not possible during attempted thrombectomy since the distal thrombi sometimes are old and adherent, which precludes successful removal (Brunner, 1979). This complicated the recovery in one of our operated patients, who subsequently developed a compartment syndrome with cessation of arterial flow leading to loss of his limb. Perhaps early fasciotomy could have changed the unfortunate outcome in this patient. Saffle et al. (1981) and Qvarfordt et al. (1983) have demonstrated that intra-compartmental pressures are increased, especially in cases with phlegmasia cerulea dolens. Although, acute thrombectomy in most instances provides a fast drop of these pressures (Qvarfordt et al., 1983), addition of crural fasciotomy is

simple and sometimes limb-saving. This procedure, therefore, should be considered at least in cases with phlegmasia cerulea dolens and when a complete vein clearance is not possible.

Although our results with thrombectomy and arteriovenous fistula have also been satisfactory concerning preservation of valvular function, additional procedures seem required to improve the long-term patency of the peripheral veins. Kiely (1973) has described a special balloon catheter for clearance of the distal veins via incision of the posterior tibial vein. Others (Brunner, 1979) have introduced guide-wires from the peripheral veins to aid distal passage of the balloon catheter, but the long-term results following these procedures are not known. Since there are multiple deep stem veins below the knee, a direct complete surgical clearance is not feasible. However, exploration and placement of the arteriovenous fistula at the popliteal level could be beneficial. This would extend the acute procedure, and technical problems with closure of a peripheral arteriovenous fistula must be solved before the routines are changed.

Management of acute iliofemoral venous thrombosis with associated chronic iliac vein obstruction

Cockett et al. (1967) claimed that iliac thrombosis secondary to iliac compression frequently results in especially severe postthrombotic sequelae. Hard data to support this concept is not available since the underlying chronic obstruction seldom is identified without surgical intervention. For the same reason the efficacy of thrombolytic treatment in these cases is not known. Thrombectomy supported by systemic or regional anticoagulation frequently is followed by rethrombosis (Mavor & Galloway, 1969; Gaylis, 1974; Lindhagen et al., 1978; Hutschenreiter et al., 1979; Provan & Rumble, 1979), but the arteriovenous fistula many times preserves a partial iliac patency and promotes the development of collaterals around the residual obstruction (Brunner, 1979; Hutschenreiter et al., 1979). In our study the arteriovenous fistula prevented rethrombosis and provided an excellent early clinical course in 3 of 6 such patients (I). The iliofemoral

segment reoccluded in the other 3 patients who all have developed postthrombotic sequelae.

Vollmar et al. (1978) have used a ring-stripper aided by venous endoscopy to remove vein spurs in conjunction with thrombectomy. Others (Cockett & Lea Thomas, 1965; Gaylis, 1974; Johnsson et al., 1974) propose direct exploration, decompression and disobliteration of the compressed vein segment but the long-term results following these procedures are not known. Exposure of the iliac veins is rather difficult, which is a draw-back in these acute situations.

In a few cases Wagner et al. (1978) and Mc Neill & Sorour (1980) have performed a cross-femoral by-pass utilizing the contralateral saphenous vein (Palma procedure) to overcome chronic obstruction in acute situations. Although long-term results are missing, this procedure seems preferential since it is simple and plastic material is not used. We utilized polytetrafluoroethylene grafts for venous reconstruction, since adequate autogenous grafts were not available, but the long-term graft patency was unacceptable. Only one of seven grafts was still patent after 2 years despite initial support by an arteriovenous fistula (III). Perhaps the fistulae were closed too early. We did not use external ring-support, the implication of which is not known. It is obvious that further development of venous prostheses and adjunctive procedures is required.

The clinical course was favourable in several of our patients operated upon with thrombectomy, arteriovenous fistula and early venous reconstruction despite graft occlusion in most cases (III). A partial iliac patency and development of collaterals obviously provided sufficient drainage, which perhaps decreased the pressure gradient over the grafts causing them to occlude. This explains why the graft occlusions occurred without causing any symptoms in most cases. The theory also implies that the iliac vein should not be transected during attempted reconstruction but the by-pass should be constructed with side-to-side anastomoses. The same conclusions have been reached by others (Gruss et al., 1981).

Since the results with early venous reconstruction are not clearly better than with reconstruction in the late postthrombotic stage (Husni, 1971; Dale, 1979), the initial procedure should be confined to acute thrombectomy with arteriovenous

fistula. This seems to provide sufficient venous drainage and clinical recovery in many cases. In cases when the arteriovenous fistula fails to prevent rethrombosis following thrombectomy severe postthrombotic sequelae are likely to develop. In those situations some kind of early venous reconstructions seems justified.

Most authorities advise against venous reconstruction in patients with vein compression by neoplasms and secondary acute thrombosis (Brunner, 1979; May & DeWeese, 1981). Continuing tumor growth and paraneoplastic changes of blood coagulability often prevent successful surgery (Brunner, 1979). However, many of these cases present with phlegmasia cerulea dolens (Brunner, 1979), which involves an immediate threat to the limb's viability. One of our early reconstructions was performed on a patient with a compressing groin liposarcoma. The reconstruction brought limb-salvage for most of the patient's remaining life. Thus, if the neoplasm is not disseminated and a reasonable survival is expected, it seems justified to attempt venous reconstruction instead of primary amputation.

Management of chronic iliac vein obstruction

Reconstruction of iliac veins will be based on the iliac compression syndrome, but similar principles could be used for reconstruction of chronic obstructions of other types. The discussion is focused on experimental development, since the clinical experience is rather limited.

Direct reconstruction

Decompressive procedures including vein dissection, repositioning of the overriding artery and resection of the underlying vertebra have been performed in small series (Wanke & Gumrich, 1950; Eufinger, 1961; Dick, 1962; Cockett & Lea Thomas, 1965; Gaylis, 1974; Johnsson et al., 1974). Others have attempted disobliteration of intraluminal vein spurs and old thrombi by balloon dilatation, ring-stripping, thrombointimectomy or patch angioplasty with or without arteriovenous fistula (Cockett & Lea Thomas, 1965; Vollmar et al., 1978; Brunner, 1979).

Many authors seem to agree that a combination of a decompressive and a disobliterative procedure would provide the best results (Cockett & Lea Thomas, 1965; May & DeWeese, 1979; Welter & Becker, 1981), but the long-term benefit with these procedures remains to be proven.

By-pass reconstruction

The classic Palma procedure is performed as a cross-femoral by-pass utilizing the long saphenous vein of the healthy limb (Palma & Esperon, 1960). Although early clinical success has been reported in 60-80% of the patients (Palma & Esperon, 1960; Husni, 1971; Dale, 1979), late phlebografic follow-up has revealed maintained graft patency in less than 50 % of the cases (Frileux et al., 1972; Hutschenreiter et al., 1979; May, 1981). Addition of a flow-increasing arteriovenous fistula has been followed by variable results (Frileux et al., 1972; Hutschenreiter et al., 1979; Gruss et al., 1979). A beneficial effect by the fistula has been recorded in less optimal conditions (May, 1981), but in what situations this should be applied is still not quite clear. It is obvious, however, that better results could be expected if reconstructions are restricted to cases with functional obstructions, obviated with increased femoral venous pressures at exercise (May, 1981; Partsch, 1981). Surgery with atraumatic technique, fine suture material, magnifying spectacles and avoidance of vein clamping has proved to prevent late anastomotic strictures (May, 1981). By using a meticulous surgical technique, adequate patient selection and arteriovenous fistula in selected cases, patency rates as good as 78-93% have been achieved (Gruss et al., 1979; May, 1981). Obviously these results are excellent, which should place this procedure as the method of choice. Still, it remains to be proven that the Palma procedure provides adequate venous drainage by demonstrating reduction of preoperative pressure gradients and long-term graft patency in a large group of patients.

Gruss et al. (1979) and Hutschenreiter et al. (1979) have implanted expanded polytetrafluoroethylene grafts with or without external ring-support in the cross-femoral, cross-iliac or ilio caval position for reconstruction of chronic iliac vein obstructions. A temporary arteriovenous fistula was used in all cases. The early graft patency was 80 - 100 % but the observations were too few and the follow-up too short to allow any definite conclusions regarding long-term results. Yet

polytetrafluoroethylene grafts could be an acceptable alternative when autogenous veins are not available, but further experimental development is required to optimize the results with vascular prostheses.

Experimental development

Venous prostheses

Sawyer et al. (1978) have analyzed factors determining graft thrombogenicity. They found that vascular prostheses with a smooth and negatively charged inner surface are likely to deposit less thrombus material on the inner surface. This is supported by the fact that the smooth and negatively charged expanded polytetrafluoroethylene (PTFE) has been most successful in the venous system (Dale & Scott, 1962; Haimovici et al., 1970; Scherck et al., 1974; Hiratzka & Wright, 1978). Patency studies with such grafts have occasionally been astonishingly good but the tested grafts have been very short, too few or placed in high flow positions (Soyer et al., 1972; Fujiwara et al., 1974; Smith et al., 1975; Fiore et al., 1982). Our experimental studies (IV) demonstrated that PTFE grafts could stay patent in the ilio caval position, but only with the aid of an arteriovenous fistula. Heparin-wetted PTFE grafts supported by a temporary arteriovenous fistula and external rings had a 6-month patency that approached the patency-rates achieved with autogenous vein grafts (I). Yet accumulation of mural thrombi in several PTFE grafts indicated future occlusion, had the observation time been longer.

It seems obvious that the creation of a non-thrombogenic graft-blood interface is the ultimate goal for research on venous prostheses. Until this goal is reached, autogenous material should be used if at all possible. The spiral vein technique described by Chiu et al. (1974) and Gloviczki et al. (1984) could provide autogenous grafts of any diameter but only short vein segments could be replaced with this technique.

Manipulation of graft characteristics

Madras et al. (1980) have demonstrated that removing air by "wetting" PTFE prostheses renders the graft surface more hydrophilic, which seems to decrease

the thrombogenicity. Takamatsu (1982) used heparin and dipyridamole solutions for the wetting procedure and achieved a rather stable release of the active substances over 1-2 weeks during immersion in running water. We studied the influence of the wetting procedure with heparin according to Takamatsu (1982) on the 3-hour thrombogenicity of PTFE prostheses. The graft patency was slightly improved, platelet deposition decreased significantly and fibrin deposition decreased slightly (IV). We also noted that heparin-wetted prostheses deposited less platelets and fibrin at the anastomoses (IV), which implies that this method could be valuable even in the prevention of late anastomotic stricture. It is not obvious if the wetting procedure itself or the incorporation of heparin was responsible for the reduced thrombogenicity, but this could be elucidated by repeated studies using prostheses that are wetted without using heparin.

More sophisticated methods for air removal and incorporation of antiaggregatory agents into vascular prostheses have been used with promising results (Najjar & Gott, 1970; Madrs et al., 1980; Noishiki, 1981). One study by Leshnower et al. (1974) failed to demonstrate any beneficial effect by the incorporation of heparin into the graft material. Although the above techniques could most likely improve the patency of venous prostheses, further development is imperative before these methods could be used in clinical practice.

Endothelial seeding

Most reports indicate that "seeding" of arterial prostheses with mechanically or enzymatically derived endothelial cells enhances graft coverage with an endothelium (Herring et al., 1979; Graham et al., 1982; Sharefkin et al., 1982). In an excellent multicenter study by Clagett et al. (1984) endothelial and sham seeded dacron prostheses implanted in the arterial system of dogs were compared blindly regarding thrombogenicity and morphological characteristics. It was noted that platelet survival, after a transient postoperative drop, increased slightly better in the dogs that had received endothelial seeded grafts, although the difference was not very striking.

Our report was the first presented series of endothelial seeding in the venous system (V). We did not find that endothelial seeding improved early patency of

PTFE grafts which has later been confirmed by Herring et al. (1984b). Our electron microscopy studies revealed that the surface of most endothelial seeded prostheses was well covered by a thin endothelial lining at 4 - 6 weeks following implantation. To our surprise, control grafts that were sham seeded with only culture medium and blood had an equally good endothelial coverage. Studies in the arterial system later have verified that sham seeded grafts develop nearly as good an endothelium as endothelial seeded grafts (Clagett et al., 1984).

It is likely that the endothelial seeding enhances graft reendothelialization, but the present technique is inadequate and does not provide sufficient protection against early thrombosis. Still, the endothelial cover that subsequently develops perhaps prevents the late occlusions, but this needs confirmation by long-term studies. Preinoculation of PTFE grafts in endothelial cell cultures has not been more successful (Herring et al., 1984b).

So far, it has not been proven that the seeded endothelial cells really generate the endothelial coverage. Perhaps other factors than the supposedly seeded endothelial cells are of importance in the development of an endothelial coverage. It may be that the culture medium and blood used for endothelial and sham seeding create an environment that enhances transformation and endothelialization with cells of other origin. This controversy could perhaps be clarified by some kind of tagging of the seeded cells.

Without any doubt, the endothelial seeding technique is complex and differing data could be due to technical problems. Proof of endothelial cell identity on the internal graft surface is difficult and has been based on electron microscopy findings (Ford, 1982). Weibel-Palade bodies are specific markers of endothelial cells, but these cell bodies are very rare and their absence does not disprove endothelial identity (Ford, 1982). Immunoelectrophoresis has been used for cell identification, but has not provided additional security in this situation (Ford, 1982; Sottiurai & Batson, 1983). Interpretation and quantitation of endothelial graft coverage is not well standardized, which also could explain divergent conclusions. Regardless, further refinement of this procedure is required before it

is adopted for clinical use. In addition endothelial behavior varies among species (Sauvage et al., 1974), and it remains to be proven that endothelial seeding is possible in humans.

Systemic antiaggregation

Anticoagulation with heparin seems to improve patency both of autogenous and synthetic grafts in the venous system, but evidence of benefit with long-term use is missing (Haimovici et al., 1970; Hiratzka & Wright, 1978; Kunlin & Kunlin, 1979). This is partly due to practical problems in providing adequate long-term anticoagulation in experimental animals. Even though platelets are accredited little importance in the development of venous thrombosis, antiplatelet drugs have been proven to enhance early graft patency (Hasegawa et al., 1973; Price Thomas et al., 1976; Gloviczki et al., 1984). Two reports on defibrination in conjunction with implantation of synthetic vein grafts have rendered divergent results concerning thrombus formation and graft patency (Browse & Clemenson, 1978; Ishimaru et al., 1981).

Since anticoagulants have proven effective in preventing venous thrombosis in other situations, it seems unjustified to perform venous reconstruction without anticoagulation even if hard data to support its use are missing. Administration of antiplatelet drugs is easier but their value in clinical practice remains to be proven before they could replace systemic anticoagulation.

Arteriovenous fistula

This adjunctive procedure mainly exerts its protective effect by increasing the blood flow velocity in the venous system. Some controversy remains regarding the need for this procedure in autogenous reconstructions (Scherck, 1974; Hiratzka et al., 1981; Gloviczki et al., 1984). Levin et al. (1971) demonstrated that the patency of autogenous vein grafts in the canine femoral position was improved if a fistula was used. Wright et al. (1977) recorded excellent patency rates with autogenous vein grafts implanted without a fistula in the same position, but their grafts was much shorter. Scheinin (1966) found the fistula to be beneficial for inferior vena cava grafts, but probably these grafts were of inadequate diameter

since they were taken from the jugular vein of the same animals. We did not find that the patency rate of autogenous vein grafts was improved by addition of a fistula (IV). All our grafts were close to isodiametric and implantation was performed with meticulous surgical technique. It seems as though the fistula is necessary for the patency of autogenous vein grafts only if the conditions are not ideal. Yet since fistula construction and closure today are simple (Plate et al., 1981), it must be justified to use a fistula even for autogenous reconstructions.

Experimental evidence is abundant on the great value of an arteriovenous fistula in improving patency of synthetic grafts in the venous system (Stansel, 1964; Scheinin, 1966; Mitsuoka & Howard, 1968; Yamaguchi et al., 1968; Scherck et al., 1974; Hiratzka & Wright, 1978; Chan et al., 1984; Gloviczki et al., 1984). We found that no PTFE prosthesis remained patent in the canine ilio caval position without initial support by an arteriovenous fistula (IV). Studies reporting good patency rates with PTFE grafts without support by a fistula are all compromised by too few and/or short graft segments tested or evaluation in high flow systems (Soyer, 1972; Fujiwara et al., 1974; Smith et al., 1975; Fiore et al., 1982). Therefore, a fistula should always be used if synthetic grafts are implanted in low flow positions in the venous system.

Notably, both we and others (Chan et al., 1984; Gloviczki et al., 1984) have observed progressive thrombus formation and occlusion of PTFE prostheses following fistula closure after 4 - 8 weeks (IV). Unpublished platelet survival studies performed in our animals at 6 months after graft implantation demonstrated a shorter platelet survival in 5 dogs with PTFE grafts (44 ± 11 h) compared to 12 dogs with autogenous vein grafts (64 ± 13 h). This indicates that prosthetic grafts remain thrombogenic even following coverage by a pseudointima, which also implies that prolonged protection against graft occlusion is required.

Support of graft wall

Venous grafts are prone to compression by surrounding organs or constrictive scar tissue because of the low intraluminal pressure in the venous system (Bryant et al., 1958; Collins et al., 1960; Scherck et al., 1974). Bryant et al. (1958) believed that the arteriovenous fistula exerts its protective effect by increasing the

intraluminal pressure. The venous pressure is increased in the peripheral veins but drops rapidly cranial to the fistula and is therefore of little importance for the graft patency (Dost, 1968; Kunlin & Kunlin, 1979).

Support of the graft wall itself has involved only a slight improvement of the patency rates of venous prostheses (Todd et al., 1963; Mitsuoka & Howard, 1968; Heydorn et al., 1977; Fiore et al., 1982). In our study the 6-month patency increased from 29 % to 60 % with external ring-support of PTFE grafts but this difference was not statistically significant (IV).

Suspension of the anastomosis with external rings has been shown to prevent the late strictures occurring at the anastomoses (Kunlin & Kunlin, 1979). This has not been used in clinical practice, but it implies that external rings supporting the graft wall should not be removed close to the anastomosis (Gruss et al., 1981).

Thus, it is likely that support of the graft wall enhances patency but larger studies are required to produce conclusive data. External support is not needed to achieve good results with autogenous vein grafts (Kunlin & Kunlin, 1979; Gloviczki et al., 1984), which corroborates the thesis that thrombogenicity is a more important factor for prolonged graft patency.

CONCLUSIONS

- Thrombectomy combined with a temporary arteriovenous fistula and systemic anticoagulation provides better early clinical results, better iliofemoral venous patency and better femoropopliteal valvular competence than anticoagulation alone in the treatment of acute iliofemoral venous thrombosis.
- Systemic anticoagulation is effective in controlling pulmonary embolism in most cases of acute iliofemoral venous thrombosis.
- With adequate patient selection and with optimal surgical technique, thrombectomy can be performed with minimal risk of creating embolism.
- Acute iliofemoral thrombectomy with arteriovenous fistula and early reconstruction of an associated chronic iliac vein obstruction using polytetrafluoroethylene grafts provide satisfactory clinical results but the long-term graft patency is poor.
- By wetting polytetrafluoroethylene grafts with heparin the acute deposition of platelets in the canine venous system is reduced.
- A temporary arteriovenous fistula does not improve the patency of autogenous vein grafts but is mandatory for retained patency of polytetrafluoroethylene grafts implanted in the canine ilio caval position.
- External ring-support only slightly enhances the patency of polytetrafluoroethylene grafts in the canine venous system.
- Heparin-wetted polytetrafluoroethylene grafts supported by external rings and a temporary arteriovenous fistula have a 6-month patency in the canine venous system is nearly as good as the patency of autogenous vein grafts.

- Endothelial seeding does not improve the early patency of polytetrafluoroethylene grafts in the canine venous system.
- Endothelial seeded polytetrafluoroethylene grafts obtain a good endothelial coverage at 4 - 6 weeks after implantation in the canine venous system but not to a greater extent than sham seeded grafts.

FUTURE PROSPECTS

- Thrombectomy with arteriovenous fistula seems to be the treatment of choice for young individuals with acute iliofemoral thrombosis, but it remains to be proven that the late postthrombotic sequelae are avoided with this procedure. The results in the peripheral veins could perhaps be improved by an even more aggressive approach. However, the benefits with any extension of the procedure must be weighed against its possible drawbacks. The more complicated a procedure the more skill and training is required to perform it.
- Patients with congestive heart failure or severe arteriosclerosis in the lower extremity are not suited for an arteriovenous fistula. For these cases it seems adequate to combine the thrombectomy with regional heparin infusions, perhaps for a prolonged time. Aged and permanently immobile individuals should be treated conservatively since anticoagulation provides satisfactory early clinical results and since prevention of late postthrombotic sequelae is not a major concern in these cases.
- Thrombolytic agents have not so far been effective and have been afflicted with too many complications to be used routinely in acute iliofemoral venous thrombosis. The theoretical preference with thrombolytic treatment, to dissolve thrombi and emboli without surgical intervention, is most appealing, however. Therefore it seems imperative to continue the research to improve the efficacy and to decrease the side-effects with thrombolysis. It could be postulated that initial surgical thrombectomy with removal of the bulk of deep venous thrombi could be optimized with regional or systemic thrombolysis to remove residual thrombi in the peripheral veins, perforators, valve pockets and in the lung arteries.
- The Palma procedure using autogenous vein grafts, meticulous technique and careful patient selection still is the procedure of choice for venous reconstruction. A temporary arteriovenous fistula is commended even for autogenous reconstructions, and this should always be used under less ideal conditions. A problem remains in those patients who lack adequate

saphenous veins. Use of spiral vein grafts or arm veins will rarely solve this problem. Presently, expanded polytetrafluoroethylene grafts supported by a temporary arteriovenous fistula seems to be the only acceptable alternative, but this prosthesis should only be used in patients with severe chronic symptoms caused by a functionally important venous obstruction. Support of the wall of the prosthesis with external rings seems to exhibit only a marginal effect but its use is supported until clearcut evidence is available.

- The search for a non-thrombogenic venous substitute must continue. Manipulation of graft characteristics, including more sophisticated methods for incorporation and release of antiaggregatory agents, could be beneficial but this needs further development. Creation of a functional endothelium on the internal graft surface seems to be the ultimate solution. Ideally, an endothelial coverage should be present already at graft implantation, and early healing of the endothelium should provide a permanent anchorage in the prosthesis and prevent development of a thickening subendothelial layer. Preinoculation of the prosthesis with endothelial cells could provide initial graft coverage, but whether a porous or a non-porous graft material offers the best healing properties in this situation is not obvious. Therefore, further improvement of the endothelial seeding technique is mandatory, before it is used in the clinical setting.
- Thus, it is obvious that future development of prophylaxis and therapy in venous disease is required, since our results are far from optimal and the suffering of the affected individuals and the economic consequences for society are immense.

ACKNOWLEDGEMENTS

I want to express my sincere gratitude to all those people who helped me with completing this thesis and to acknowledge my special indebtedness to Mrs Anita Wallin Gjöres, Mrs Karin Olsson and Ms Lena Henriksson for their skillful secretarial assistance.

This study was supported by grants from the Thorsten and Elsa Segerfalk Foundation for Medical Research and Education, from the Swedish National Association against Heart and Chest Diseases, and from the Rappaport Clinician-Investigator Fellowship Program.

REFERENCES

- Albrechtsson U, Andersson J, Einarsson E, Eklöf B, Norgren L. Streptokinase treatment of deep vein thrombosis and the postthrombotic syndrome. Follow-up evaluation of venous function in the post-thrombotic legs. *Arch Surg* 116:33-7, 1981a.
- Albrechtsson U, Einarsson E, Eklöf B. Femoral vein pressure measurements for evaluation of venous function in patients with postthrombotic iliac veins. *Cardiovasc Intervent Radiol* 4:43-50, 1981b.
- Aleman J & Helmig L. Indikation zur chirurgischen Behandlung der tiefen Bein- und Beckenvenenthrombosen. *Zentralbl Chir* 102:1121-31, 1977.
- Andriopoulos A, Wirsing P, Bötticher R. Results of iliofemoral venous thrombectomy after acute thrombosis. Report on 165 cases. *J Cardiovasc Surg* 23:123-4, 1982.
- Arnesen A, Heilo A, Jakobsen E, Ly B, Skaga E. A prospective study of streptokinase and heparin in the treatment of deep vein thrombosis. *Acta Med Scand* 203:457-63, 1978.
- Baker LW. The treatment of established iliofemoral deep vein thrombosis with streptokinase. *S Afr Med J* 52:64-8, 1977.
- Barner HB, Willman VL, Kaiser GC, Hanlon CR. Thrombectomy for iliofemoral venous thrombosis. *JAMA* 208:2442-6, 1969.
- Bauer G. Thrombosis: Early diagnosis and abortive treatment with heparin. *Lancet* 1:447-54, 1946.
- Baumann G. Indikation, Technik und Ergebnisse der Thrombektomie. *Chirurg* 47:112-7, 1976.
- Bertelsen S. Surgical management of iliofemoral thrombophlebitis. *Acta Chir Scand* 135:149-54, 1969.
- Bradham RR & Buxton JT. Thrombectomy for acute iliofemoral venous thrombosis. *Surg Gynecol Obstet* 119:1271-5, 1964.
- Britt LG. Iliofemoral veno-occlusive disease. Results with thrombectomy in 16 cases. *Am Surg* 32:103-6, 1966.
- Brockman SK & Vasko JS. Phlegmasia cerulea dolens. *Surg Gynecol Obstet* 121:1347-56, 1965.
- Browse NL & Clemenson G. Vein surgery during defibrinogenation. *Br J Surg* 65:452-5, 1978.
- Browse NL, Clemenson C, Lea Thomas M. Is the postphlebotic leg always postphlebotic? Relation between phlebographic appearances of deep-vein thrombosis and late sequelae. *Br Med J* 281:1167-70, 1980.

Brunner U. Die femoroiliakale Thrombose als evolutive Venenobstruktion: Probleme in chirurgischer Sicht. *Vasa* 3:22-6, 1974.

Brunner U. Acute thrombosis. Surgery of acute femoroiliac phlebothrombosis. In May R ed: *Surgery of the veins of the leg and pelvis*. Stuttgart, Georg Thieme Publ., 1979:105-25.

Brunner U & Wirth W. Spätresultate nach Thrombektomie bei Iliofemoralvenenthrombose im klinisch-radiologischen Vergleich. *Schweiz Med Wschr* 101:1327-34, 1971.

Bryant MF, Lazenby WD, Howard JM. Experimental replacement of short segments of veins. *Arch Surg* 76:289-93, 1958.

Capdevila JM, Bongera F, Luque M, Estevan J, Vaquero F. Ilio-caval thrombectomy. *J Cardiovasc Surg*, Special issue 443, 1975.

Chan EL, Bardin JA, Bernstein EF. Inferior vena cava bypass: Experimental evaluation of externally supported grafts and initial clinical application. *J Vasc Surg* 1:675-80, 1984.

Chiu CJ, Terzis J, MacRae ML. Replacement of superior vena cava with the spiral composite vein graft. *Ann Thorac Surg* 17:555-60, 1974.

Clagett GP, Burkel WE, Sharefkin JB et al. Platelet reactivity in vivo in dogs with arterial prostheses seeded with endothelial cells. *Circulation* 69:632-9, 1984.

Cockett FB & Lea Thomas M. The iliac compression syndrome. *Br J Surg* 52:816-21, 1965.

Cockett FB, Lea Thomas M, Negus D. Iliac vein compression. Its relation to iliofemoral thrombosis and the post-thrombotic syndrome. *Br Med J* 2:14-9, 1967.

Collins GJ, Rich NM, Scialla S, Andersen CA, McDonald PT. Coagulation abnormalities in patients with arterial, venous, and combined arterial and venous thromboses. *Arch Surg* 112:1347-51, 1977.

Common HH, Seaman AJ, Rösch J, Porter JM, Dotter CT. Deep vein thrombosis treated with streptokinase or heparin. *Angiology* 27:645-54, 1976.

Dale WA. Reconstructive venous surgery. *Arch Surg* 114:1312-8, 1979.

Dale WA & Scott HW. Grafts of the venous system. *Surgery* 53:52-74, 1963.

Delin A, Swedenborg J, Hellgren M, Jacobsson H, Nilsson E. Thrombectomy and arteriovenous fistula for iliofemoral venous thrombosis in fertile women. *Surg Gynecol Obstet* 154:69-73, 1982.

Denck H. Operative Therapie (Thrombektomie, Schirmfilter, Cavaligatur). *Langenbecks Arch Chir* 345:381-8, 1977.

Dewanjee MK, Rao SA, Didisheim P. Indium-111 tropolone, a new high-affinity platelet label: preparation and evaluation of labeling parameters. *J Nucl Med* 22:981-7, 1981.

DeWeese JA. Thrombectomy for acute iliofemoral venous thrombosis. *J Cardio-vasc Surg* 5:703-12, 1964.

DeWeese JA. Iliofemoral venous thrombectomy. In Bergan JJ & Yao JST eds: *Venous Problems*. Chicago, Year Book Medical Publ., 1978:421-34.

Dhall DP, Dawson AA, Mavor GE. Problems of resistant thrombolysis and early recurrent thrombosis in streptokinase therapy. *Surg Gynecol Obstet* 146:15-20, 1978.

Dick V. Klinik und Therapie der Venensperre am Confluens der beiden gemeinsamen Iliacalvenen. *Langenbecks Arch Chir* 301:573-7, 1962.

Dodd H & Cockett FB eds. The pathology and surgery of the veins of the lower limb. Iliofemoral thrombosis. Edinburgh, Churchill Livingstone, 1976:226-43.

Dost K. Druck und Flussgeschwindigkeit in der Vene bei plastischem Venenersatz. *Angiologica* 5:271-9, 1968.

Duckert F, Müller G, Nyman D et al. Treatment of deep vein thrombosis with streptokinase. *Br Med J* 1:479-81, 1975.

Dumanian AV, Santschi DR, Park K, Walker AP, Frahm CJ. Cross-over saphenous vein graft combined with a temporary femoral arteriovenous fistula. A case report. *Vasc Surg* 2:116-22, 1968.

Edwards WS. A-V fistula after venous reconstruction. A simplified method of producing and obliterating the shunt. *Ann Surg* 196:669-71, 1982.

Edwards WH, Sawyers JL, Foster JH. Iliovomoral venous thrombosis: Reappraisal of thrombectomy. *Ann Surg* 171:961-70, 1970.

Egeblad K, Bojsen - Möller J, Jacobsen B. Kirurgisk behandling af dyb venös trombose. *Nord Med* 83:438-43, 1970.

Einarsson E, Albrechtsson U, Eklöf B et al. Results of venous thrombectomy and temporary AV fistula (abstr.). *Acta Chir Scand*, Suppl 506:32, 1981.

Einarsson E, Eklöf B, Kuenzig M et al. Scanning electron-microscopy and Evans blue staining for assessing endothelial trauma and reconstruction after venous treatment. *Scan Electron Microsc* 1:273-8, 1984.

Eklöf B, Gjörös J-E, Lohi A, Staszkiwicz W, Norgren L. Spontaneous rupture of liver and spleen with severe intra-abdominal bleeding during streptokinase treatment of deep venous thrombosis. *Vasa* 6:369-71, 1977.

- Elliot MS, Immelman EJ, Jeffery P et al. A comparative randomized trial of heparin versus streptokinase in the treatment of acute proximal venous thrombosis: an interim report of a prospective trial. *Br J Surg* 66:838-43, 1979.
- Eriksson I, Hiortonn T, Thorén L. Venous thrombectomy. *Acta Chir Scand* 133:289-92, 1967.
- Eufinger H, Diethelm L, May E. Röntgenologische und Operationsbefunde bei chronischer Beckenvenensperre und ihre Bedeutung für die Operationsindikation. *Brun's Beitr Klin Chir* 203:152-70, 1961.
- Fiore AC, Brown JW, Cromartie RS et al. Prosthetic replacement for the thoracic vena cava. *J Thorac Cardiovasc Surg* 84:560-8, 1982.
- Fogarty TJ, Dennis D, Krippaehne WW. Surgical management of iliofemoral venous thrombosis. *Am J Surg* 112:211-7, 1966.
- Fontaine R & Tuchmann L. The role of thrombectomy in deep venous thromboses. *J Cardiovasc Surg* 5:298-312, 1964.
- Ford JW. Methods for macroscopic and microscopic analysis of experimentally implanted prosthetic vascular grafts. In Stanley JC ed: *Biologic and synthetic vascular prostheses*. New York, Grune & Stratton, 1982:257-76.
- Frileux C, Pillot-Bienayme P, Gillot C. Bypass of segmental obliterations of iliofemoral venous axis by transposition of saphenous vein. *J Cardiovasc Surg* 13:409-14, 1972.
- Fujiwara Y, Cohn LH, Adams D, Collins JJ. Use of Gortex grafts for replacement of the superior and inferior venae cavae. *J Thorac Cardiovasc Surg* 67:774-9, 1974.
- Gaylis H. A rational approach to venous thrombectomy. *Surg Gynecol Obstet* 138:864-8, 1974.
- Gjöres JE. The incidence of venous thrombosis and its sequelae in certain districts in Sweden (thesis). *Acta Chir Scand, Suppl* 206, 1956.
- Gloviczki P, Hollier LH, Cherry KJ, Pairolero PC, Gale SS, Schirger A. Phlegmasia cerulea dolens: The continuing morbidity. *Inter Angio* 1:127-34, 1982.
- Gloviczki P, Hollier LH, Dewanjee MK, Trastek VF, Hoffman EA, Kaye MP. Experimental replacement of the inferior vena cava: Factors affecting patency. *Surgery* 95:657-66, 1984.
- Gmelin E & Theiss W. Repeated phlebographic examination during and after fibrinolytic therapy with streptokinase and urokinase. *Cardiovasc Radiol* 1:157-64, 1978.
- Goto H, Wada T, Matsumoto A, Matsumura H, Soma T. Iliofemoral venous thrombectomy. *J Cardiovasc Surg* 21:341-6, 1980.

Gottlob R & May R. Der Frühverschluss der Palma-Operation, Vorbeugung durch Anwendung einer endothelschonenden Operationstechnik. *Vasa* 6:263-9, 1977.

Graham LM, Burkel WE, Ford JW, Vinter DW, Kahn RH, Stanley JC. Expanded polytetrafluoroethylene vascular prostheses seeded with enzymatically derived and cultured canine endothelial cells. *Surgery* 91:550-9, 1982.

Graham LM, Vinter DW, Ford JW, Kahn RH, Burkel WE, Stanley JC. Cultured autogenous endothelial cell seeding of prosthetic vascular grafts. *Surg Forum* 30:204-6, 1979.

Greenfield LJ, Zocco J, Wilk J, Schroeder TM, Elkins RC. Clinical experience with the Kim-Ray Greenfield vena cava filter. *Ann Surg* 185:692-7, 1977.

Gruss JD, Bartels D, Kawai S, Karadedos C, Tsafandakis E. Application of plastic material in the Palma operation. *Angio* 1:51-7, 1979.

Gutschi S. Die chirurgische Behandlung der akuten Beckenvenenthrombose. *Zentralbl Chir* 107:1447-51, 1982.

Hafner CD, Cranley JJ, Krause RJ, Strasser ES. Venous thrombectomy: Current status. *Ann Surg* 161:411-7, 1965.

Haimovici H, Hoffert PW, Zinicola N, Steinman C. An experimental and clinical evaluation of grafts in the venous system. *Surg Gynecol Obstet* 131:1173-86, 1970.

Haller JA & Abrams BL. Use of thrombectomy in the treatment of acute iliofemoral venous thrombosis in forty-five patients. *Ann Surg* 158:561-9, 1963.

Hasegawa T, Matsumoto H, Yamamoto M, Fuse K, Mizuno A, Saigusa M. Prosthetic replacement of superior vena cava. *Ann Surg* 106:848-50, 1973.

Havig Ö. Deep vein thrombosis and pulmonary embolism (thesis). *Acta Chir Scand Suppl* 478, 1977.

Herring M, Gardner A, Glover J. A single-staged technique for seeding vascular grafts with autogenous endothelium. *Surgery* 84:498-504, 1978.

Herring M, Gardner A, Glover J. Seeding human arterial prostheses with mechanically derived endothelium. *J Vasc Surg* 1:279-84, 1984a.

Herring M, Gardner A, Peigh P et al. Patency in canine inferior vena cava grafting: Effects of graft material, size, and endothelial seeding. *J Vasc Surg* 1:877-87, 1984b.

Heyden B. Endoscopy in thrombectomy. In May R & Weber J eds: *Pelvic and abdominal veins. Progress in diagnosis and therapy.* Amsterdam, Excerpta Medica, 1981:231-2.

Heydorn WH, Zajtchuk R, Miller J, Schuchmann GF. Gore-Tex grafts for replacement of the superior vena cava. *Ann Thorac Surg* 23:539-44, 1977.

Hiratzka LF, Doty DB, Wright CB. Newer tissue synthetic grafts in canine femoral veins. *J Surg Res* 31:324-31, 1981.

Hiratzka LF & Wright CB. Experimental and clinical results of grafts in the venous system: A current review. *J Surg Res* 25:542-61, 1978.

Horsch S, Zehle A, Eisenhardt HJ, Landes T, Pichlmaier H. Chirurgische Behandlung der akuten Bein- und Beckenvenenthrombose. *Med Klin* 74:101-8, 1979.

Husni EA. Venous reconstruction in postphlebotic disease. *Circulation* 43-44 (Suppl 1):147-50, 1971.

Hutschenreiter S, Vollmar J, Loeprecht H, Abendschein A, Rödl W. Rekonstruktive Eingriffe am Venensystem - Spätergebnisse unter kritischer Bewertung funktioneller und gefäßmorphologischer Kriterien. *Chirurg* 50:555-63, 1979.

Höjensgård IC. Sequelae of deep thrombosis in the lower limbs. *Angiology* 3:42-7, 1952.

Ishimaru S, Berglin E, Hansson H-A, Teger-Nilsson A-C, William-Olsson G. Haemostatic clot formation at anastomosis of synthetic venous graft in defibrinogenated dogs: A scanning electron microscopic study. *Thrombos Haemostas* 45:276-81, 1981.

Johansson E, Ericson K, Zetterquist S. Streptokinase treatment of deep venous thrombosis of the lower extremity. *Acta Med Scand* 199:89-94, 1976.

Johansson E, Nordlander S, Zetterquist S. Venous thrombectomy in the lower extremity - Clinical, phlebographic and plethysmographic evaluation of early and late results. *Acta Chir Scand* 139:511-6, 1973.

Johnsson K-Å, Göthman B, Nordström S. The iliac compression syndrome. *Acta Radiol* 15:539-45, 1974.

Kaiser GC, Murrar RC, William VL, Hanlon CR. Iliofemoral thrombectomy for venous occlusion. *Arch Surg* 90:574-7, 1965.

Kakkar VV, Flanc C, Howe CT, O'Shea M, Flute PT. Treatment of deep vein thrombosis. A trial of heparin, streptokinase, and arvin. *Br Med J* 1:806-10, 1969.

Karp RB & Wylie EJ. Recurrent thrombosis after iliofemoral venous thrombectomy. *Surg Forum* 17:147, 1966.

Kiely PE. A new venous thrombectomy technique. *Br J Surg* 60:850-2, 1973.

Kistner RL, Ball JJ, Nordyke RA, Freeman GC. Incidence of pulmonary embolism in the course of thrombophlebitis of the lower extremities. *Am J Surg* 124:169-76, 1972.

Kistner RL & Sparkuhl MD. Surgery in acute and chronic venous disease. *Surgery* 85:31-43, 1979.

Kitainik E & Quiros RS. Thrombectomy and caval interruption. J Cardiovasc Surg 13:440-5, 1972.

Kriessmann A & Rupp N. Natürlicher Verlauf der venösen Drainage-Insuffizienz bei Becken- und tiefer Beinvenenthrombose. Vasa 6:124-7, 1977.

Kriessmann A, Theiss W, Lutitsky L, Wirtzfeld A, Seifert W, Grünberg G. Fibrinolytische Therapie bei tiefen Venenthrombosen der oberen und unteren Extremität. Fortschr Med 95:858-66, 1977.

Krug A, Lehmann K, Zaborsky F. Modifizierte temporäre AV-Fistel beim venösen suprapubischen Cross-Over-Shunt wegen einseitiger Beckenvenensperre. Chirurg 45:389-90, 1974.

Kunlin J. Le rétablissement de la circulation veineuse par greffe en cas d'oblitération traumatique ou thrombophlébitique. Greffe de 18 cm entre la veine saphène interne et la veine iliaque externe. Thrombose après trois semaines de perméabilité. Mem Acad Chir 79:109-10, 1953.

Kunlin J & Kunlin A. Experimental venous surgery. In May R ed: Surgery of the veins of the leg and pelvis. Stuttgart, Georg Thieme Publ., 1979:37-75.

Köpf RI & Stahlknecht CD. Temporäre Arterialisierung der Venenstrombahn nach operativer Thrombektomie. Bruns' Beitr Klin Chir 220:719-24, 1973.

Lansing AM & Davis WM. Five-year follow-up study of iliofemoral venous thrombectomy. Ann Surg 168:620-8, 1968.

Leriche R. Traitement chirurgical des suites éloignées des phlébites et des grands oedèmes non médicaux des membres inférieurs. Bull Mem Soc Nat Chir 53:187-95, 1927.

Leshnower AC, Shumacker HB, Shariatzadeh AN. Experimental studies with synthetic venous bypass grafts, including a new experimental model. Am J Surg 128:392-7, 1974.

Leu HJ. Die Spontanrekanalisation thrombotischer Venenverschlüsse in pathologisch-anatomischer Sicht. Zentralbl Phleb 7:4-6, 1968.

Levin PM, Rich NM, Hutton JE, Barker WF, Zeller JA. Role of arteriovenous shunts in venous reconstruction. Am J Surg 122:183-91, 1971.

Lindhagen J, Haglund M, Haglund U, Holm J, Scherstén T. Ileo-femoral venous thrombectomy. J Cardiovasc Surg 19:319-27, 1978.

Linton RR. The post-thrombotic ulceration of the lower extremity: Its etiology and surgical treatment. Ann Surg 138:415-33, 1953.

Little JM, Loewenthal J, Mills FH. Venous thrombo-embolic disease. Br J Surg 53:657-67, 1966.

- Läwen A. Ueber Thrombektomie bei Venenthrombose und Arteriospasmus. *Zentralbl Chir* 64:961-8, 1937.
- Madras PN, Johnson WR, Ward CA. Enhancement of thrombus formation by vascular prostheses. *Can J Surg* 23:544-6, 1980.
- Mahorner H, Castleberry JW, Coleman WO. Attempts to restore function in major veins which are the site of massive thrombosis. *Ann Surg* 146:510-22, 1957.
- Maillard J-N & Gillot C. Artérialisation du segment veineux thrombectomisé dans le traitement chirurgical tardif d'une thrombose de la veine cave inférieure. *Presse Med* 78:2417-19, 1970.
- Mansfield AO, Carmichael JHE, Parry EW. Thrombectomy employing continuous radiological control. *Br J Surg* 58:119-23, 1971.
- Matsubara J, Ban I, Nakata Y et al. Long-term follow-up results of the iliofemoral venous thrombosis. *J Cardiovasc Surg* 17:234-9, 1976.
- Mavor GE, Dhall DP, Dawson AA et al. Streptokinase therapy in deep-vein thrombosis. *Br J Surg* 60:468-74, 1973.
- Mavor GE & Galloway JMD. Collaterals of the deep venous circulation of the lower limb. *Surg Gynecol Obstet* 125:561-71, 1967.
- Mavor GE & Galloway JMD. Iliofemoral venous thrombosis. *Br J Surg* 56:43-59, 1969.
- May R. The Palma operation with Gottlob's endothelium-preserving technique. In May R & Weber J eds: *Pelvic and abdominal veins. Progress in diagnosis and therapy.* Amsterdam, Excerpta Medica, 1981:192-7.
- May R & Thurner J. Ein Gefässsporn in der v. iliaca com. sin als wahrscheinliche Ursache der überwiegend linksseitigen Beckenvenenthrombose. *Ztsch Kreisf Forsch* 45:912-22, 1956.
- May R & DeWeese JA. Surgery of pelvic veins. In May R ed: *Surgery of the veins of the leg and pelvis.* Stuttgart, Georg Thieme Publ., 1979:158-76.
- McNeill AD & Sorour NN. Veno-venous internal saphenous crossover graft for phlegmasia caerulea dolens. *Br J Surg* 67:877-8, 1980.
- Metz L & Weber H. Die chirurgische Behandlung der akuten Becken-Beinvenenthrombose. *Zentralbl Chir* 105:1211-5, 1980.
- Mitsuoka H & Howard JM. Experimental grafting of the inferior vena cava. *J Cardiovasc Surg* 9:190-4, 1968.
- Nachbur B & Wiesmann A. Können die Behandlungsergebnisse bei tiefer Thrombophlebitis verbessert werden durch Kombination von chirurgischer Thrombektomie und regionaler Fibrinolyse? *Helv Chir Acta* 44:791-6, 1977.

- Najjar FB & Gott VL. The use of small-diameter Dacron grafts with wall-bonded heparin for venous and arterial replacement: Canine studies and preliminary clinical experience. *Surgery* 68:1053-63, 1970.
- Nedjabat T, Birtel FJ, Neuhaus G, Thelen M, Schmidt I. Ätiologie, Diagnostik und operative Behandlung der akuten Bein-, Becken- und unteren Hohlvenenthrombose. *Zentralbl Chir* 104:529-40, 1979.
- Negus D & Cockett FB. Femoral vein pressures in post-phlebitic iliac vein obstruction. *Br J Surg* 54:522-5, 1967.
- Nissl R. Acute thrombosis. Roentgenologic aspects. In May R ed: *Surgery of the veins of the leg and pelvis*. Stuttgart, Georg Thieme Publ., 1979:96-104.
- Noishiki Y, Nagaoka S, Kikuchi T, Mori Y. Application of porous heparinized polymer to vascular graft. *Trans Am Soc Artif Intern Organs* 27:213-8, 1981.
- Norgren L & Gjöres JE. Venous function in previously thrombosed legs. A follow-up study of streptokinase-treated patients. *Acta Chir Scand* 143:421-4, 1977.
- O'Donnell TF, Browse NL, Burnand KG, Lea Thomas M. The socioeconomic effects of an iliofemoral venous thrombosis. *J Surg Res* 22:483-8, 1977.
- Palma EC. Early thrombectomy in phlebothrombosis. *J Cardiovasc Surg* 9:161-9, 1968.
- Palma EC & Esperon R. Vein transplants and grafts in the surgical treatment of the postphlebitic syndrome. *J Cardiovasc Surg* 1:94-107, 1960.
- Paquet KJ, Popov S, Egli H. Richtlinien und Ergebnisse der konsequenten fibrinolytischen Therapie der Phlegmasia caerulea dolens. *Dtsch Mediz Wochenschr* 1:903-4, 1970.
- Partsch H. The clinical relevance of pelvic vein obstructions. In May R & Weber J eds: *Pelvic and abdominal veins. Progress in diagnosis and therapy*. Amsterdam, Excerpta Medica, 1981:166-71.
- Plate G, Albrechtsson U, Einarsson E, Eklöf B. Technical problems in thrombectomy with a temporary arteriovenous fistula in the treatment of acute iliofemoral venous thrombosis. In May R & Weber J eds: *Pelvic and abdominal veins. Progress in diagnosis and therapy*. Amsterdam, Excerpta Medica, 1981:224-31.
- Poilleux J, Chermet J, Bigot J-M, Deliere T. Les thromboses veineuses ilio-femorales recentes. *Ann Chir* 29:713-9, 1975.
- Price Thomas JM, Glynn MFX, Rickwood AMK, Gough MH. Grafting of the major veins: the value of anti-thrombotic drugs to maintain patency. *Br J Surg* 63:189-95, 1976.
- Provan JL & Rumble EJ. Re-evaluation of thrombectomy in the management of iliofemoral venous thrombosis. *Can J Surg* 22:378-81, 1979.

Purtscheller W. Anesthesia for venous surgery. In May R ed: Surgery of the veins of the leg and pelvis. Stuttgart, Georg Thieme Publ., 1979:76-81.

Qvarfordt P, Eklöf B, Ohlin P. Intramuscular pressure in the lower leg in deep vein thrombosis and phlegmasia cerulea dolens. *Ann Surg* 197;450-3, 1983.

Röder OC, Lorentzen JE, Buchardt Hansen HJ. Venous thrombectomy for ilio-femoral thrombosis. *Acta Chir Scand* 150:31-4, 1984.

Saffle JR, Maxwell JG, Warden GD, Jolley SG, Lawrence PF. Measurement of intramuscular pressure in the management of massive venous occlusion. *Surgery* 89:394-7, 1981.

Sauvage LR, Berger KE, Wood SJ et al. Interspecies healing of porous arterial prostheses. Observations 1960 to 1974. *Arch Surg* 109:698-705, 1974.

Sawyer PN, Stanczewski B, Lucas TR, Srinivasan S, Ramasamy N, Kirschenbaum D. Physical chemistry of the vascular interface. In Sawyer PN & Kaplitt MJ eds: Vascular grafts. New York, Appleton-Century-Crofts, 1978:53-75.

Scheinin TM. Temporary arteriovenous fistula in experimental replacement of the inferior vena cava. *Acta Chir Scand Suppl* 357:286-90, 1966.

Scherck JP, Kerstein MD, Stansel HC. The current status of vena caval replacement. *Surgery* 76:209-33, 1974.

Schmitt HE. Phlebography in thrombosis of the pelvic veins and the inferior v. cava: visualisation and significance of collateral pathways. In May R & Weber J eds: Pelvic and abdominal veins. Progress in diagnosis and therapy. Amsterdam, Excerpta Medica, 1981:12-5.

Schnitzler J. Ueber die chirurgische Behandlung der Varicen nebst Bemerkungen zur postoperativen Phlebitis. *Wien Med Wschr* 61:241-5, 1911.

Senn A & Althaus U. Die chirurgische Behandlung der Phlebothrombose. *Chirurg* 44:193-7, 1973.

Sevitt S. Pathology and pathogenesis of deep vein thrombi. In Bergan JJ & Yao JST eds: Venous problems. Chicago, Year Book Medical Publ., 1978:257-78.

Sharefkin JB, Latker C, Smith M, Cruess D, Clagett GP, Rich NM. Early normalization of platelet survival by endothelial seeding of dacron arterial prostheses in dogs. *Surgery* 92:385-93, 1982.

Smith DE, Hammon J, Anane-Sefah J, Richardson RS, Trimble C. Segmental venous replacement: A comparison of biological and synthetic substitutes. *J Thorac Cardiovasc Surg* 69:589-98, 1975.

Smith GW. Therapy of iliofemoral venous thrombosis. *Surg Gynecol Obstet* 121:1298-302, 1965.

- Sottiturai VS & Batson RC. Role of myofibroblasts in pseudointima formation. *Surgery* 94:792-801, 1983.
- Soyer T, Lempinen M, Cooper P, Norton L, Eiseman B. A new venous prosthesis. *Surgery* 72:864-72, 1972.
- Spatenka J, Kalny J, Hosek P. Shifts in external iliac venous pressure under local and general anaesthesia. *Cor Vasa* 21:347-52, 1979.
- Stansel HC. Synthetic inferior vena cava grafts. *Arch Surg* 89:1096-101, 1964.
- Steinman C, Alpert J, Haimovici H. Inferior vena cava bypass grafts. *Arch Surg* 93:747-54, 1966.
- Stephens GL. Current opinion on iliofemoral venous thrombectomy. *Am Surg* 42:108-15, 1976.
- Takamatsu T. Absorption and desorption of heparin and persantin in expanded polytetrafluoroethylene tubes (abstr.), Eighth Annual Meeting of the Society for Biomaterials, Orlando, FL, 1982.
- Theiss W, Wirtzfeld A, Fink U, Maubach P. The success rate of fibrinolytic therapy in fresh and old thrombosis of the iliac and femoral veins. *Angiology* 34:61-9, 1983.
- Todd RS, Sive EB, DeJode LR, Danese C, Howard JM. Replacement of segments of the venous system. *Arch Surg* 87:136-40, 1963.
- Vollmar J, Loeprecht H, Hutschenreiter S. Rekonstruktive Eingriffe am Venensystem. *Chirurg* 49:296-302, 1978.
- Vollmar J & Laubach K. Die Rekonstruktion unilateraler Beckenvenenverschlüsse. *Aktuelle Chirurgie* 5:79-84, 1970.
- Wagner O, Piza F, Müller-Hartburg W. Zur chirurgischen Therapie der Beckenvenenthrombose in der Schwangerschaft. *Wien Klin Wschr* 85:17-9, 1973.
- Wanke R & Gumrich H. Chronische Beckenvenensperre. *Zentralbl Chir* 75:1302-12, 1950.
- Watz R & Savidge GF. Rapid thrombolysis and preservation of valvular venous function in high deep vein thrombosis. *Acta Med Scand* 205:293-8, 1979.
- Weber J. Sanguinous measurement of venous blood pressure in the pelvic vein spur. In May R & Weber J eds: *Pelvic and abdominal veins. Progress in diagnosis and therapy*. Amsterdam, Excerpta Medica, 1981:153-65.
- Weber J, Wirth W, Brunner U. Die frische Iliofemoralvenenthrombose. Ergebnisse der 3-Stufen-Phlebographie vor und nach operativ behandelter frischer Iliofemoralvenenthrombose. *Fortschr Röntgenstr* 119:666-83, 1973.

Welter HF & Becker HM. Therapy of the pelvic venous spur and postoperative follow-up. In May R & Weber J eds: Pelvic and abdominal veins. Progress in diagnosis and therapy. Amsterdam, Excerpta Medica, 1981:172-7.

Widmer LK, Madar G, Schmitt HE, Duckert F, DaSilva MA, Müller G. Heparin oder Thrombolyse in der Behandlung der tiefen Beinvenenthrombose. Vasa 3:422-32, 1974.

Wilson H & Britt LG. Surgical treatment of iliofemoral thrombosis. Ann Surg 165:855-9, 1967.

Wright CB, Hobson RW, Giordano JM, DeWitt PL, Rich NM. Acute femoral venous occlusion. J Cardiovasc Surg 18:523-9, 1977.

Yamaguchi A, Eguchi S, Iwasaki T, Asano K. The influence of arteriovenous fistulae on the patency of synthetic inferior vena caval grafts. J Cardiovasc Surg 9:99-103, 1968.

Young AE, Lea Thomas M, Browse NL. Comparison between sequelae of surgical and medical treatment of venous thromboembolism. Br Med J 4:127-30, 1974.

THROMBECTOMY WITH
TEMPORARY ARTERIOVENOUS
FISTULA: THE TREATMENT OF
CHOICE IN ACUTE ILIOFEMORAL
VENOUS THROMBOSIS

G. PLATE, M.D.
E. EINARSSON, M.D.
P. OHLIN, M.D., Ph.D.
R. JENSEN, M.D., Ph.D.
P. QVARFORDT, M.D., Ph.D.
and
B. EKLOF, M.D., Ph.D.
Helsingborg, Sweden

From the Department of Surgery, University of Lund (Dr. Einarsson), and the Departments of Surgery (Drs. Plate, Qvarfordt, and Eklof), Clinical Physiology (Dr. Ohlin), and Diagnostic Radiology (Dr. Jensen), Helsingborg County Hospital, Helsingborg, Sweden.

Reprinted from
JOURNAL OF VASCULAR SURGERY
St. Louis

Vol. 1, No. 6, pp. 867-876, November, 1984
(Copyright © 1984, by Society for Vascular
Surgery and North American Chapter for
Cardiovascular Surgery)
(Printed in the U.S.A.)

Thrombectomy with temporary arteriovenous fistula: The treatment of choice in acute iliofemoral venous thrombosis

G. Plate, M.D., E. Einarsson, M.D., P. Ohlin, M.D., Ph.D., R. Jensen, M.D., Ph.D., P. Qvarfordt, M.D., Ph.D., and B. Eklöf, M.D., Ph.D., *Helsingborg, Sweden*

The treatment of choice in acute iliofemoral venous thrombosis is still controversial. This prospective randomized study compares the results of conventional anticoagulation of 32 patients with the results obtained in 31 patients undergoing acute thrombectomy combined with a temporary arteriovenous fistula and anticoagulation. Early complications were few in both treatment groups, and significant pulmonary embolism developed in only one conservatively treated patient. At 6-month follow-up in all surviving patients, leg swelling, varicose veins, and venous claudication were more frequent after conservative treatment. Only 7% (2 of 27) of these patients were completely free from postthrombotic symptoms compared with 42% (10 of 24) of the operated patients ($p < 0.005$). Contrast phlebography demonstrated an excellent venous outflow through the iliofemoral segment in 35% (9 of 26) of the conservatively treated and in 76% (16 of 21) of the operated patients ($p < 0.025$). Open femoropopliteal veins with competent valves were recorded in 26% (7 of 27) in the conservative group and in 52% (12 of 23) in the thrombectomy group ($p < 0.05$). Thus thrombectomy combined with arteriovenous fistula decreases early symptoms and preserves venous outflow and valvular function better than conservative treatment. This procedure is therefore recommended for young patients with acute iliofemoral thrombosis to avoid development of incapacitating postthrombotic sequelae. (*J VASC SURG* 1984; 1:867-876.)

Loss of life from pulmonary embolism, loss of limb from venous gangrene, and loss of capacity for work from postthrombotic sequelae are the three major threats in acute iliofemoral venous thrombosis. Since the 1950s anticoagulation with heparin and coumarin derivatives has been the standard treatment to avoid these complications. Surgical thrombectomy and induced thrombolysis with streptokinase or urokinase were introduced in the 1960s and the 1970s¹⁻⁶ but still are not generally accepted.

Anticoagulation, thrombolysis, and surgical treatment are all effective in preventing pulmonary embolism.^{2,6-10} In severe cases with impending ve-

nous gangrene, thrombectomy with systemic anticoagulation is generally recommended.¹¹⁻¹⁵ Controversy still remains regarding which mode of treatment most effectively prevents the late postthrombotic sequelae after iliofemoral venous thrombosis.

The incidences of chronic leg swelling, varicose veins, leg pain during exercise (venous claudication), and leg ulcers following iliofemoral venous thrombosis have in previous reports varied considerably with either treatment.^{7,16-20} This great variation in late results is probably due to differences in patient selection, follow-up time, and subjectivity in the evaluation of the patients' symptoms. More objective criteria are therefore necessary in assessing which treatment is likely to provide the best long-term results. For this purpose contrast phlebography is considered most reliable since radiographic evidence of venous outflow obstruction and valvular incompetence correlates well with later development of postthrombotic sequelae.^{4,13,16,21,22}

Acute thrombectomy combined with a temporary arteriovenous fistula has proved effective in achieving and maintaining iliofemoral vein patency and in relieving early symptoms.²²⁻²⁴ Objective and controlled evaluation of this procedure has not been

From the Department of Surgery, University of Lund (Dr. Einarsson), and the Departments of Surgery (Drs. Plate, Qvarfordt, and Eklöf), Clinical Physiology (Dr. Ohlin), and Diagnostic Radiology (Dr. Jensen), Helsingborg County Hospital, Helsingborg, Sweden.

Presented at the Thirty-eighth Annual Meeting of the Society for Vascular Surgery, Atlanta, Ga., June 7-8, 1984.

Supported by The Thorsten and Elsa Segerfalk Foundation for Medical Research and Education and by The Salus' Fifty-Year Foundation for Medical Research.

Reprint requests: Gunnar Plate, M.D., Dept. of Surgery, Helsingborg County Hospital, S-25187 Helsingborg, Sweden.

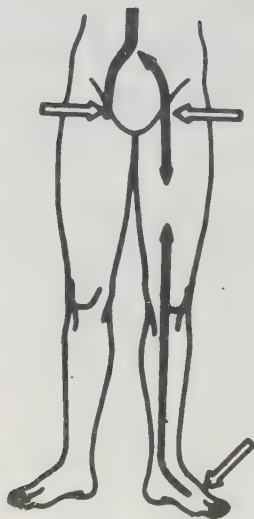


Fig. 1. Technique of three-point contrast phlebography performed in clinically suspected acute iliofemoral venous thrombosis.

performed previously. The present study was designed to compare the results obtained by thrombectomy combined with arteriovenous fistula and systemic anticoagulation with the results obtained by anticoagulation alone in the treatment of acute iliofemoral venous thrombosis. This article emphasizes the phlebographic results as predictive of the development of late postthrombotic sequelae.

MATERIAL AND METHODS

From July 1, 1979, to June 30, 1982, 63 patients admitted to Helsingborg County Hospital and to the University of Lund, Sweden, with acute iliofemoral venous thrombosis met the following criteria for inclusion into the present study:

1. Deep venous thrombosis with proximal extension above inguinal ligament but below caval bifurcation
2. Swelling of entire leg for less than 7 days
3. Present pedal pulses
4. Neither anticoagulation nor surgery contraindicated

Table I. Characteristics of 58 patients in study of acute iliofemoral venous thrombosis

	Conservative treatment (n = 31)	Thrombectomy and AVF* (n = 27)
Age (years; median and range)	63 (15-79)	63 (18-80)
Sex (male/female)	13/18	12/15
Site of thrombus (right/left)	8/23	6/21
Duration of leg swelling (days; median and range)	1 (0-5)	2 (0-7)

*AVF = arteriovenous fistula.

5. No history or sign of congestive heart failure
6. No verified metastatic malignant disease
7. Not pregnant
8. Patient normally ambulating

Four of the patients had significant leg pain with bluish skin discoloration, as in phlegmasia cerulea dolens, but had pedal pulses present. A likely etiology of the thrombus was established in each case, including neoplasm (11 patients), limb injuries or immobilization (10), coagulation abnormality such as decreased vessel wall fibrinolysis or increased blood factor VIII (nine), recent unrelated surgery (seven), previous calf thrombosis (seven), oral contraception (four), and recent delivery (three). The thrombus was considered idiopathic in 12 patients.

The extent of the thrombus was delineated with so-called three-point phlebography (Fig. 1). Ascending phlebograms demonstrated no filling in any of the deep veins of the whole leg in all but five patients. Contrast injection into the common femoral vein of the affected leg was attempted in all patients to demonstrate thrombus involvement above the inguinal ligament. Inability to aspirate blood from the groin veins (in 16 patients) was accepted as an indirect indication of iliofemoral thrombosis, although this segment was not visualized. Extension of the thrombus into the vena cava was excluded by a free cephalad flow of contrast injected into the contralateral femoral vein.

All patients were informed of the character and risk of the disease as well as of therapeutic possibilities. After giving informed consent, the patients were randomized to conservative treatment or to acute thrombectomy with arteriovenous fistula.

Thirty-two patients were allocated to the conservative treatment group and were started on continuous intravenous infusion of heparin sodium (Kabi Vitrum AB, Stockholm, Sweden). A bolus of 5000 units was followed by 500 U/kg/24 hr, ad-

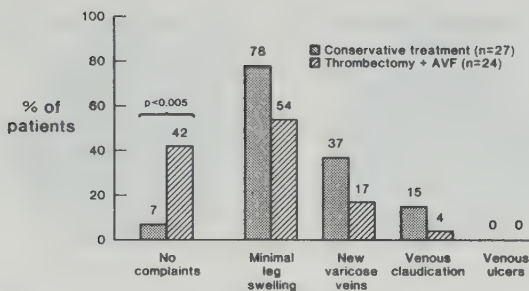


Fig. 2. Clinical status in 51 patients 6 months following acute iliofemoral venous thrombosis. AVF = arteriovenous fistula.

justed to an activated partial thromboplastin time of 60 to 120 seconds, which was continued for at least 5 days and until effective oral anticoagulation (thrombotest results of 5% to 15%) with dicumarol (Apekumarol, Ferrosan, AB, Malmö, Sweden) had been achieved. Oral anticoagulation was discontinued after 6 months unless the workup had revealed any coagulation abnormality. One of the patients in whom puncture of a groin vein had failed was subsequently excluded from the study. Review of his initial ascending phlebogram revealed faint but complete filling of the iliac vein, excluding thrombotic involvement above the inguinal ligament.

Thirty-one patients were allocated to the group undergoing acute thrombectomy with arteriovenous fistula. These patients were anticoagulated in the same way as the conservatively treated patients. Operations were performed under general intubation anesthesia. The long saphenous vein, the common femoral vein, and the superficial femoral artery of the affected leg were exposed through a vertical groin incision. The common femoral vein was incised transversely, and thrombectomy with the use of a venous Fogarty balloon catheter was performed under fluoroscopy control and positive end-expiratory pressure applied by the ventilator. Manual compression of the leg was also performed to remove distal thrombi. The long saphenous vein was divided 10 cm from the saphenofemoral junction, and an arteriovenous fistula was constructed by anastomosing the cranial end of the saphenous vein to the side of the superficial femoral artery. A No. 5 French infant-feeding catheter was introduced into the fistula through a saphenous vein tributary and left in place for 24 hours for completion phlebography and control phlebography on the first postop-

erative day. The arteriovenous fistula was closed after 4 to 6 weeks under local anesthesia only. The technical details of thrombectomy and fistula construction have been described previously.²⁵ In four cases in whom the initial phlebogram had not visualized the iliofemoral segment, it was discovered during the operation that the top of the thrombus was located immediately below the inguinal ligament. These patients were excluded from the study.

The characteristics of the 58 patients remaining in the study are given in Table I. In comparing the two treatment groups, no significant difference was found concerning age and sex of the patients and site of the thrombus, but the duration of leg swelling was slightly shorter in the conservatively treated group.

Follow-up was performed 6 months after the initial thrombosis. Development of postthrombotic sequelae including leg swelling, varicose veins, leg ulcers, and venous claudication was evaluated. Bilateral ascending and retrograde contrast phlebography was performed as described by Gullmo.²⁶ The phlebographic status of the iliofemoral segment (common and external iliac and common femoral veins) was defined as excellent (normal iliofemoral segment or a short cranial stenosis at the crossing of the common iliac artery), fair (short cranial occlusion or extensive stenosis), or bad (long or complete occlusion including the iliac bifurcation). The presence of dilated prepubic, internal iliac, presacral or ascending lumbar collateral vessels was also evaluated. The No. 5 French (outer diameter) polyethylene catheter used for contrast injection was connected to a pressure transducer (Siemens-Elema AB, Solna, Sweden), and the intraluminal pressure

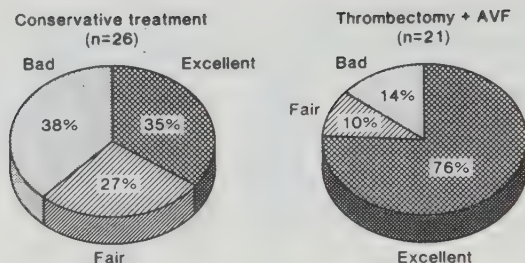


Fig. 3. Phlebographic status of iliofemoral segment in 47 patients 6 months following acute iliofemoral venous thrombosis. AVF = arteriovenous fistula.

in both common femoral veins was measured in the supine position at rest and during 20 forceful dorsiflexions of the foot as described by Albrechtsson et al.²⁷ The femoropopliteal segment was studied after contrast injection into a superficial foot vein with a tourniquet applied above the ankle. Valvular competence in this segment was evaluated during Valsalva's maneuver in the supine position after contrast injection into the common femoral vein. Doppler ultrasound equipment was used to evaluate the presence of venous reflux in the popliteal vein after calf compression and during Valsalva's maneuver in the erect position.

Statistical evaluation of qualitative data was performed by chi-square analysis. The two-tailed Student's *t*-test was used for analyzing quantitative data.

RESULTS

Both conservatively and surgically treated patients experienced a rapid decrease in leg swelling. The difference in calf circumference when comparing the two legs decreased during the first week from 4.3 ± 2.0 cm (mean $\pm$ SD) to 2.6 ± 1.8 cm in the conservative group and from 3.8 ± 2.2 to 2.0 ± 1.8 cm in the surgical group. The hospital stay ranged from 5 to 23 days (median 9 days) in the conservative group and 7 to 35 days (median 11 days) in the surgical group.

Early complications were infrequent in both treatment groups. Recurrent symptomatic pulmonary embolism occurred in only one conservatively treated patient. This was controlled by plication of the infrarenal vena cava. No severe bleeding complications were recorded in either group, but three patients in the surgical group developed local wound

hematoma. Control phlebography on the first postoperative day was performed in 23 operated patients by contrast injection through the retained infant-feeding catheter. Early reocclusion was detected in three patients (13%). Clearance of the cranial iliac vein had been impossible in two of these patients, and attempted rethrombectomy in one of them was also unsuccessful. Leg gangrene developed in one additional patient, who had presented with phlegmasia cerulea dolens, despite a technically successful iliofemoral thrombectomy. Clearance of the distal veins was impossible and intracompartmental pressures in the calf remained elevated (above 40 mm Hg). The initial clinical course of this patient was favorable but deteriorated suddenly on the fifth postoperative day when the heparin infusion was discontinued. The iliofemoral segment was at this time still patent, but repeated surgical attempts at restoring distal arterial and venous flow were unsuccessful, resulting in amputation above the knee.

Clinical follow-up after 6 months was possible in 27 conservatively treated and 24 operated patients (Fig. 2). Six patients died from metastatic malignant disease before follow-up. Moderate leg swelling, new varicose veins, and leg pain during exercise (venous claudication) were more frequent in the conservatively treated patients, although these differences were not statistically significant. No patient in either group had leg ulcers. Two (7%) conservatively treated and 10 (42%) operated patients were completely free of symptoms related to the previous thrombosis. This difference was statistically significant ($p < 0.005$).

Follow-up phlebography was performed in all but one patient who refused this examination.

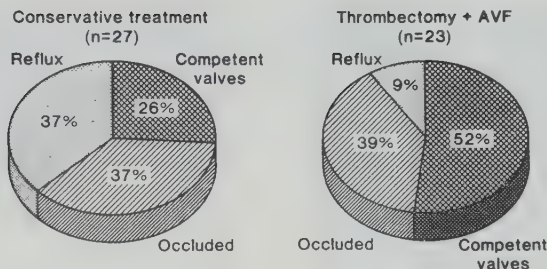


Fig. 4. Phlebographic status of the femoropopliteal segment in 50 patients 6 months following acute iliofemoral venous thrombosis. AVF = arteriovenous fistula.

Puncture of the femoral vein was unsuccessful, and ascending phlebograms from a foot vein did not provide adequate information on the iliofemoral segment in one conservatively treated and two operated patients. These three patients have subsequently been studied with an isotope imaging technique, suggesting that their iliofemoral veins are patent. Phlebographic information on the status of the iliofemoral segment was thus available in 26 conservatively treated and 21 operated patients (Fig. 3). An excellent result was noted in nine (35%) conservatively and 16 (76%) surgically treated patients. A fair result was recorded in seven (27%) of the conservatively treated and in two (10%) of the operated patients. The result was considered bad in 10 (38%) of the conservatively treated and in three (14%) of the operated patients. Statistical analysis revealed that the results demonstrated by phlebographic studies of the iliofemoral segment were significantly better in the surgical group than in the conservatively treated group ($p < 0.025$). Dilated pelvic collaterals were recorded in 17 (65%) of the conservatively treated and in five (24%) of the operated patients ($p < 0.005$).

Measurement of femoral venous pressure was performed in 33 patients. The pressure increase during exercise was 3.2 ± 0.5 mm Hg (mean $\pm$ SEM) in patients with an excellent phlebographic result but statistically greater ($p < 0.001$) both in patients with a fair (8.0 ± 0.9 mm Hg) and in patients with a bad result (10.0 ± 2.0 mm Hg). In 18 conservatively treated patients the pressure increase during exercise was 6.7 ± 1.1 mm Hg and in 15 operated patients, 4.4 ± 0.9 mm Hg ($0.1 < p < 0.2$).

The femoropopliteal segment was evaluated with phlebography in 27 conservatively treated and in 23

operated patients (Fig. 4). Venous occlusions were found in 10 patients (37%) in the conservative and in nine patients (39%) in the surgical group. Of the patients who had an open femoropopliteal segment, it was noted that 41% (7 of 17 patients) in the conservative group and 86% (12 of 14 patients) in the surgical group had competent valves preventing reflux of contrast material during Valsalva's maneuver. This difference was statistically significant ($p < 0.05$).

Evaluation of venous reflux with Doppler equipment correlated well with the phlebographic findings of valvular competence. Doppler reflux was present in all patients with open veins and valvular incompetence but not in patients with competent valves.

Combining the phlebographic findings of both the iliofemoral and femoropopliteal segments, it was found that nine patients had a completely open venous system with competent valves (Fig. 5). The femoral venous pressure increase during exercise was less than 5 mm Hg, Doppler reflux was absent, and all were completely free of symptoms. These nine patients all belonged to the surgical group.

DISCUSSION

Acute deep venous thrombosis is treated conservatively in most institutions. Previous reports of anticoagulation treatment in acute iliofemoral thrombosis have demonstrated that initial lysis is rare.^{2,10,17,28} The incidence of recanalization of the iliofemoral segment, development of sufficient collateral flow, and preservation of femoropopliteal valvular competence after conservatively treated iliofemoral thrombosis is not well known because of a low incidence of follow-up phlebography in most

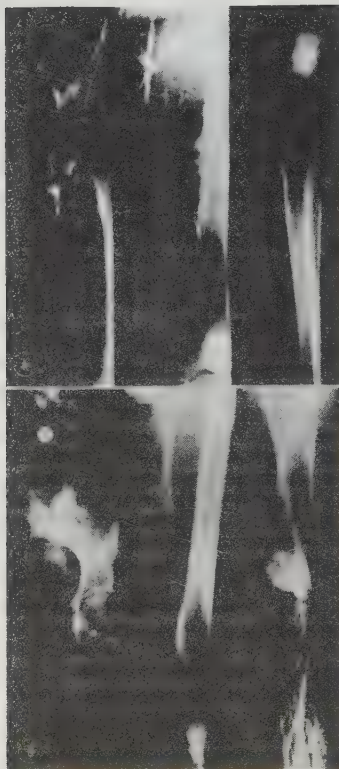


Fig. 5. Ascending phlebograms obtained before, A, and 6 months after, B, venous thrombectomy combined with temporary arteriovenous fistula in a 35-year-old woman with acute thrombosis of entire left leg developing 1 week after cholecystectomy.

series. Better information is available regarding the development of postthrombotic sequelae recorded in 36% to 90%^{3,7,17,29} of conservatively treated patients. In the present study phlebographic follow-up was performed in over 90% of the patients, demonstrating an excellent iliofemoral segment in 35% and increased pelvic collateral vessels in the other 65% of the conservatively treated patients. The femoropopliteal segment was recorded as open in 63% of the patients, with competent valves in 26%. These results explain why most patients with conservatively

treated iliofemoral thrombosis experience a favorable initial course. The long-term results, especially in patients with residual venous obstruction and valvular incompetence, are more doubtful.

Several reports have described complete or partial lysis in a high percentage of deep venous thromboses treated with streptokinase or urokinase.* In these studies many patients had thrombi limited to the calf or femoropopliteal segments. Considering only iliofemoral thromboses, the results with thrombolytic therapy have been less impressive with initial, often incomplete thrombolysis achieved in 38% to 85% of the patients.[†] Rethrombosis after discontinued thrombolysis has been reported in nearly 50% of the patients despite continued anticoagulation.^{6,32} In addition, thrombolytic therapy is complicated by severe bleeding in 5% to 14% of the patients,^{4,17,28,30} and hepatic and splenic rupture have occasionally been described.^{30,33} In about one third of the patients, thrombolytic therapy is impossible because of recent surgery, gastrointestinal bleeding, cerebrovascular accident, pregnancy, hypertension, or presence of antibodies.^{17,28,32} Late iliofemoral patency rates of 50% to 63% with postthrombotic sequelae developing in 42% to 70% of patients after thrombolytic therapy have been reported by Johansson et al.,⁴ Elliott et al.,¹⁷ and Albrechtsson et al.³⁴ Valvular competence after iliofemoral thrombosis was recorded by Elliot et al.¹⁷ in 30% of patients. These results are thus not markedly better than results obtained with anticoagulation alone.

In most cases of iliofemoral thrombosis, surgical thrombectomy is initially successful if the thrombus is less than 1 week old.^{9,13,15,35} The reports of Brunner and Wirth,¹⁶ Hutschenreiter et al.,²² Fogarty et al.,³⁶ and Johansson et al.³⁷ provide acceptable information on phlebographic long-term results. Their late iliofemoral patency rates were 21% to 71%, and valvular competence was recorded in 0% to 29% of the patients. Postthrombotic sequelae developed in 18% to 81% of the patients. Thus thrombectomy seems not to provide better protection against late postthrombotic sequelae or better venous outflow or valvular competence than does conservative treatment. This is most likely the result of a high incidence of rethrombosis following thrombectomy.^{22,37,38}

Postoperative infusion of heparin into the thrombectomized iliac vein to prevent early reocclusion has been used by Mahorner et al.,⁵ Edwards et al.,⁸

*References 2, 4, 6, 10, 17, 30.

†References 2, 4, 17, 30, 31.

Mavor and Galloway,¹⁵ Lindhagen et al.,³⁹ and Provan and Rumble⁴⁰ with good clinical results. Their early iliofemoral patency rates were 72% to 93%, whereas the late patency rates dropped to 49% to 67% as recorded by Mavor and Galloway¹⁵ and Lindhagen et al.³⁹ None of the studies provided information of late valvular competence. These results suggest that rethrombosis still occurs after discontinuation of the local heparin infusion. Thus it seems necessary to protect thrombectomized veins even after the immediate postoperative period. Experimental studies on reendothelialization following thrombectomy indicate that endothelial healing takes at least 4 weeks, during which time protection against rethrombosis is probably necessary.⁴¹

Based on experimental studies by Kunlin and Kunlin,⁴² a flow-increasing arteriovenous fistula has been used in conjunction with iliofemoral thrombectomy.* With this method the incidence of early rethrombosis has been decreased to below 20%.²² Late iliofemoral patency rates of 60% to 83% and postthrombotic sequelae in 0% to 17% of the patients have been reported.^{13,22-24,44} The present study demonstrates that thrombectomy with a temporary arteriovenous fistula is more effective than conservative treatment in providing relief of early symptoms (Fig. 2). Phlebography demonstrated early rethrombosis in only 13% of the operated patients. The venous outflow through the iliofemoral segment at 6 months following thrombectomy with an arteriovenous fistula was still excellent in 76% of the patients (Fig. 3). Although femoropopliteal occlusion was present in about one third of the patients, valvular competence was preserved in one half of the patients (Fig. 4). These results obtained with thrombectomy and arteriovenous fistula are thus better than previously reported results with other treatment and also significantly better than our results with conservative treatment.

Interpretation of our results is somewhat compromised by 16 initial phlebograms that did not demonstrate the iliofemoral portion of the deep venous thrombus. In four of these cases the iliofemoral thrombus was later verified at surgery, but in five other patients the thrombus did not extend above the inguinal ligament and these patients were excluded from the study. One of these patients died before follow-up, leaving in the study six conservatively treated patients with inconclusive initial phlebograms. Three of these patients had excellent

follow-up phlebograms with no signs of previous thrombosis in the iliofemoral segment. Exclusion of the patients with inconclusive initial phlebograms would have rendered the results even more in favor of surgical treatment and therefore would not have changed our conclusions.

One of our operated patients who presented with phlegmasia cerulea dolens had persistently elevated intracompartmental pressures in the calf, which subsequently led to amputation of the leg above the knee. Quarfordt et al.⁴⁵ have previously demonstrated that extensive deep venous thrombosis causes increased intracompartmental pressures and decreased tissue perfusion. In retrospect, initial fasciotomy and/or exploration of the distal veins might have saved the leg of this patient. It is unlikely, however, that conservative treatment would have been more successful.

Our few failures with surgical treatment were related to the presence of a preexisting obstruction of the cranial iliac vein or to incomplete clearance of the distal veins. Presently we know of no diagnostic test, including contrast phlebography, that in most cases could identify patients with an underlying chronic iliac vein obstruction causing the acute thrombosis. Perhaps a more aggressive approach with early reconstruction of the iliac vein, fasciotomy, exploration of the lower leg veins, and fistula placement more caudally would be indicated in certain circumstances. We routinely performed the present procedure because of its simplicity, with the long saphenous vein readily available for use as an arteriovenous fistula. We do not believe that sacrifice of the long saphenous vein impairs venous drainage, since this vein almost invariably is involved in the thrombotic process and would remain occluded or incompetent if left in place.

Use of an arteriovenous fistula has also been criticized because of problems related to closure of the fistula. We have developed a technique that significantly simplifies this procedure that was performed without complications in all our patients.²⁸

Thus conventional anticoagulation provides good control of pulmonary embolism and relief of acute symptoms in most cases of iliofemoral venous thrombosis. This therapy therefore is recommended if late postthrombotic sequelae are not a major concern (in chronically immobile patients or patients with a limited life expectancy) and whenever surgery is contraindicated. Thrombectomy combined with a temporary arteriovenous fistula should be considered in all young individuals with acute iliofemoral venous thrombosis to avoid later development of

*References 13, 22-24, 43, 44.

postthrombotic sequelae. Surgical thrombectomy is the best method to clear the deep veins, and the arteriovenous fistula effectively prevents postoperative rethrombosis. If an arteriovenous fistula is contraindicated (in patients with congestive heart failure or occlusive arterial disease), postoperative local heparin infusion is an acceptable alternative. Valvular competence is better preserved with thrombectomy and arteriovenous fistula than with anticoagulation alone and, perhaps, also better than with thrombolysis. It therefore is likely that even the late postthrombotic sequelae will be ameliorated with this procedure, but only long-term follow-up will provide this information.

REFERENCES

- DeWeese J. Thrombectomy for acute iliofemoral venous thrombosis. *J Cardiovasc Surg* 1964; 48:703-12.
- Duckert F, Müller G, Nyman D, et al. Treatment of deep vein thrombosis with streptokinase. *Br Med J* 1975; 1:479-81.
- Fontaine R, Tuchmann L. The role of thrombectomy in deep venous thromboses. *J Cardiovasc Surg* 1964; 5:298-312.
- Johansson E, Ericson K, Zetterquist S. Streptokinase treatment of deep venous thrombosis of the lower extremity. *Acta Med Scand* 1976; 199:89-94.
- Mahomer H, Castleberry JW, Coleman WO. Attempts to restore function in major veins which are the site of massive thrombosis. *Ann Surg* 1957; 146:510-22.
- Mavor GE, Dhall DP, Dawson AA, et al. Streptokinase therapy in deep-vein thrombosis. *Br J Surg* 1973; 60:468-74.
- Denck H. Operative Therapie (Thrombektomie, Schirmfiter, Cavaligatur). *Langenbecks Arch Chir* 1977; 345:381-8.
- Edwards WH, Sawyers JL, Foster JH. Iliofemoral venous thrombosis: Reappraisal of thrombectomy. *Ann Surg* 1970; 171:961-70.
- Kistner RL, Sparkuhl MD. Surgery in acute and chronic venous disease. *Surgery* 1979; 85:31-43.
- Widmer LK, Madar G, Schmitt HE, et al. Heparin oder Thrombolysen in der Behandlung der tiefen Beinvenenthrombose. *Vasa* 1974; 3:422-32.
- Andriopoulos A, Wirsing P, Böttcher R. Results of iliofemoral venous thrombectomy after acute thrombosis. Report on 165 cases. *J Cardiovasc Surg* 1982; 23:123-4.
- Brockman SK, Vasko JS. Observations on the pathophysiology and treatment of phlegmasia cerulea dolens with special reference to thrombectomy. *Am J Surg* 1965; 109:485-92.
- Horsch S, Zehle A, Eisenhardt HJ, et al. Chirurgische Behandlung der akuten Bein- und Beckenvenenthrombose. *Med Klin* 1979; 74:101-8.
- Matsubara J, Hirai M, Kawai S, et al. Treatment of iliofemoral venous occlusion. *J Cardiovasc Surg* 1982; 23:256-60.
- Mavor GE, Galloway JMD. Iliofemoral venous thrombosis. Pathological considerations and surgical management. *Brit J Surg* 1969; 56:45-58.
- Brunner U, Wirth W. Spätergebnisse nach Thrombektomie bei Iliofemoralvenenthrombose im klinisch-radiologischen Vergleich. *Schweiz Med Wochenschr* 1971; 101:1327-34.
- Elliot MS, Immelman EJ, Jeffery P, et al. A comparative randomized trial of heparin versus streptokinase in the treatment of acute proximal venous thrombosis: An interim report of a prospective trial. *Br J Surg* 1979; 66:838-43.
- Goto H, Wada T, Matsumoto A, et al. Iliofemoral venous thrombectomy. Follow-up studies of 88 patients. *J Cardiovasc Surg* 1980; 21:341-6.
- Lansing AM, Davis WM. Five-year follow-up study of iliofemoral venous thrombectomy. *Ann Surg* 1968; 168:620-8.
- O'Donnell TF, Browne NL, Burnand KG, et al. The socioeconomic effects of an iliofemoral venous thrombosis. *J Surg Res* 1977; 22:483-8.
- Baumann G. Indikation, Technik und Ergebnisse der Thrombektomie. *Chirurg* 1976; 47:112-7.
- Hutschenreiter S, Vollmar J, Locprecht H, et al. Rekonstruktive Eingriffe am Venensystem—Spätergebnisse unter kritischer Bewertung funktioneller und gefäßmorphologischer Kriterien. *Chirurg* 1979; 50:555-63.
- Delin A, Swedenborg J, Hellgren M, et al. Thrombectomy and arteriovenous fistula for iliofemoral venous thrombosis in fertile women. *Surg Gynecol Obstet* 1982; 154:69-73.
- Einarsson E, Albrechtsson U, Eklof B, et al. Iliofemoral vein thrombosis—Results of venous thrombectomy and temporary AV-fistula (Abstract). *Acta Chir Scand (Suppl)* 1981; 506:32.
- Plate G, Albrechtsson U, Einarsson E, et al. Technical problems in thrombectomy with a temporary arteriovenous fistula in the treatment of acute iliofemoral vein thrombosis. In: May R, Weber J, eds. *Pelvic and abdominal veins*. Amsterdam: Excerpta Medica, 1981:224-30.
- Gullmo A. On the technique of phlebography of the lower limb. *Acta Radiol* 1955; 46:603-20.
- Albrechtsson U, Einarsson E, Eklof B. Femoral vein pressure measurements for evaluation of venous function in patients with post-thrombotic iliac veins. *Cardiovasc Intervent Radiol* 1981; 4:43-50.
- Arnesen H, Heilo A, Jakobsen E, et al. A prospective study of streptokinase and heparin in the treatment of deep vein thrombosis. *Acta Med Scand* 1978; 203:457-63.
- Browne NL, Clemenson G, Thomas ML. Is the postphlebotic leg always postphlebotic? Relation between phlebographic appearances of deep-vein thrombosis and late sequelae. *Br Med J* 1980; 281:1167-70.
- Kriessmann VA, Theiss W, Lutitsky L, et al. Fibrinolytische Therapie bei tiefen Venenthrombosen der oberen und unteren Extremität. *Fortschr Med* 1977; 95:858-66.
- Gmelin E, Theiss W. Repeated phlebographic examination during and after fibrinolytic therapy with streptokinase and urokinase. *Cardiovasc Radiol* 1978; 1:157-64.
- Dhall DP, Dawson AA, Mavor GE. Problems of resistant thrombolysis and early recurrent thrombosis in streptokinase therapy. *Surg Gynecol Obstet* 1978; 146:15-20.
- Eklof B, Gjores J-E, Lohi A, et al. Spontaneous rupture of liver and spleen with severe intra-abdominal bleeding during streptokinase treatment of deep venous thrombosis. *Vasa* 1977; 6:369-71.
- Albrechtsson U, Andersson J, Einarsson E, et al. Streptokinase treatment of deep vein thrombosis and the post-thrombotic syndrome. Follow-up evaluation of venous function in the post-thrombotic legs. *Arch Surg* 1981; 116:33-7.
- Bertelsen S. Surgical management of iliofemoral thrombophlebitis. *Acta Chir Scand* 1969; 135:149-54.
- Fogarty TJ, Dennis D, Krippaehne WW. Surgical management of iliofemoral venous thrombosis. *Am J Surg* 1966; 112:211-7.

37. Johansson E, Nordlander S, Zetterquist S. Venous thrombectomy in the lower extremity: Clinical, phlebographic and plethysmographic evaluation of early and late results. *Acta Chir Scand* 1973; 139:511-6.
38. Karp RB, Wylie EJ. Recurrent thrombosis after iliofemoral venous thrombectomy. *Surg Forum* 1966; 12:147.
39. Lindhagen J, Haglund M, Haglund U, et al. Iliofemoral venous thrombectomy. *J Cardiovasc Surg* 1978; 19:319-27.
40. Provan JL, Rumble EJ. Re-evaluation of thrombectomy in the management of iliofemoral venous thrombosis. *Can J Surg* 1979; 22:378-81.
41. Einarsson E, Eklof B, Kuenzig M, et al. Scanning electron-microscopy and Evans blue staining for assessing endothelial trauma and reconstruction after venous treatment. *Scan Electron Microsc* 1984; 1:273-8.
42. Kunlin J, Kunlin A. Experimental venous surgery. In: May R, ed. *Surgery of the veins of the leg and pelvis*. Stuttgart: Georg Thieme Publishers, 1979:37-75.
43. Brunner U. Die femoroliakale Thrombose als evolutive Venenobstruktion: Probleme in chirurgischer Sicht. *Vasa* 1974; 3:22-7.
44. Poilleux J, Chermet J, Bigot J-M, et al. Les thromboses veineuses ilio-femorales recentes. A propos de 27 cas traites chirurgicalement. *Ann Chir* 1975; 29:713-9.
45. Qvarfordt P, Eklof B, Ohlin P. Intramuscular pressure in the lower leg in deep venous thrombosis and phlegmasia cerulea dolens. *Ann Surg* 1983; 197:450-3.

DISCUSSION

Dr. W. Sterling Edwards (Albuquerque, N.M.). I would like to ask one question. How late can you still do a thrombectomy in a patient with acute thrombosis? We found that if one waits more than 72 hours after the initial procedure, the adherent thrombus often cannot be completely removed.

I would like to suggest a simpler method for closing an arteriovenous (AV) fistula. At the time of the operation when an AV fistula is created with the use of a short segment of vein, or even a short segment of prosthetic graft, one should leave a loop of nonabsorbable thread wrapped around the fistula. This loop of thread can then be brought through the sartorius muscle to a small skin incision. The two ends of this suture are threaded over a small button. The button is simply to help find the thread at the second stage. One can then, under local anesthesia, remove the button, pull on the thread, tighten the loop, and obliterate the fistula very easily in about 10 minutes with almost no dissection. Surgically closing these fistulas is not easy, discouraging surgeons from using AV fistulas in venous operations. If one uses a synthetic graft to produce an AV fistula, the loop sometimes does not completely obliterate the fistula, but the radiologist can easily complete the closure with a tiny balloon embolus.

Dr. Peter Samuels (Tarzana, Calif.). In 1983 Bo Eklof presented a similar paper at the Annual Meeting of the Society of Clinical Vascular Surgeons. I was impressed by the technique and the results. Shortly after I was asked to see a 25-year-old woman who was 5 days post partum and had a swollen left leg. The findings suggested iliofemoral thrombophlebitis and this was confirmed by a phlebogram.

The result was completely successful. We noted both in the operative phlebogram and in the follow-up phlebogram that there was a congenital stenosis, which, as others have pointed out, is not infrequent in the spontaneous occurrences of iliofemoral thrombophlebitis. I would like to know from the authors how they manage patients with congenital stenoses.

Dr. Bernard H. Nachbur (Bern, Switzerland). I would like to point out that, in this prospective, randomized study, the authors have not answered the question of whether an adjuvant temporary AV fistula offers added benefit to meticulous venous thrombectomy alone, which by itself produces gratifying results in properly selected patients with thrombosis of no more than 3 to 4 days' duration. We have also experienced dramatic results with venous thrombectomy in two patients with renal transplants in whom clot removal led to immediate recovery of renal function and hence graft salvage.

I have one more remark to make and two questions to ask. Widmer and associates in Basel have shown in their 5-year follow-up of well over 100 patients treated with systemic fibrinolysis that the hemodynamic and clinical results were good only if prior treatment had resulted in complete success with radiologic evidence of complete patency but not in cases with only partial clearance. A follow-up period of 6 months is not yet sufficiently long to prove that the postphlebotic syndrome can be avoided by surgery. Are the authors going to carry on their follow-up as long as 5 years?

Do they believe that iliofemoral thrombectomy is relevant at all if the popliteal valve is intact? Nicolaides maintains that no postphlebotic syndrome will develop if the popliteal valve is not involved, but one can argue that patients with obstruction of the iliofemoral axis are prone to new episodes of deep venous thrombosis with later involvement of the popliteal valve.

Dr. John J. Bergan (Chicago, Ill.). Dr. Plate, is there a better placement for the AV fistula, perhaps at the ankle, to ensure clearing of the entire venous tree and perhaps prevention of venous gangrene?

Dr. Makis J. Tsapogas (Stony Brook, N.Y.). I noted with interest the reported findings on the patients of Dr. Plate and his colleagues 6 months after iliofemoral venous thrombosis. We also believe that this time interval is rather short to evaluate fully the impact of the postphlebotic syndrome. In addition, it should be taken into consideration that creation of an AV fistula does inevitably expose the

patient to two surgical procedures with possible side effects and complications.

In patients with massive acute iliofemoral venous thrombosis that may endanger the integrity of the extremity, our method is as follows: First, we perform thrombectomy. As the small veins are almost invariably involved in the thrombotic process, we additionally institute regional fibrinolytic therapy. Our technique for regional administration consists of introducing an intra-arterial catheter, the tip of which is placed at the distal popliteal artery. This approach has two distinct advantages: (1) The required amount of the enzyme is small, thus minimizing the side effects. (2) It is delivered in the distal venous tree where thrombectomy is not feasible or effective. This therapy also reduces the incidence of rethrombosis, which frequently follows thrombectomy.

The results obtained are encouraging, with reduction both in the immediate complications and the postthrombotic sequelae. Longer follow-up and larger series are needed for definitive conclusions.

Have the authors applied this combined therapy, and if so, what were their results?

Dr. Dieter Raithel (Erlangen, Germany). Our experience with this procedure at the surgical clinic in Erlangen is not as favorable. We have now performed about 140 venous thrombectomies, and we could follow up the first 100. The aim of the operation, which was to prevent primary embolism and postthrombotic syndrome, was not achieved. In our series the mortality rate was 5%; four patients died in the perioperative period from pulmonary embolism.

At 6 months follow-up, 57.1% of the operated patients were completely free of symptoms and 14.3% had minor symptoms; but after 1 year, only 20% were free of symptoms, and after 2.5 years follow-up, no patient was free of symptoms. Thus our data show that the longer the time from the operation the greater the proliferative sequelae, for example, postthrombotic syndrome.

In the near future we will publish these data as compared with a conservatively treated group in our clinic; the data will show a lower incidence of pulmonary embolism and positive symptoms such as leg swelling and venous claudication with conservative treatment. In our experience there is now only a limited indication for venous thrombectomy in acute venous thrombosis.

Dr. Plate (closing). **Dr. Edwards**, the outcome of ve-

nous thrombectomy is of course better if performed early. Organization of the thrombus with ingrowth of fibroblasts from the vein wall after 5 to 7 days frequently leads to postoperative rethrombosis despite the use of an AV fistula.

A congenital stenosis usually located in the cranial left common iliac vein is, as Dr. Samuels pointed out, another common cause of rethrombosis following thrombectomy. Presently we know of no reliable method of identifying these patients before surgery. The use of an adjunctive AV fistula could in these cases keep the distal iliac vein patent and perhaps promote the development of collaterals. We have in a few such cases performed early venous bypass procedures, but the results have not yet been evaluated.

Dr. Bergan, we have certainly considered a more aggressive surgical approach to clear the distal veins also and to preserve the popliteal valve, the importance of which was also stressed by Dr. Nachbur. However, in this study we elected to be consistent with our procedures to allow reliable comparison with conservative treatment.

Dr. Edwards, your technique of fistula closure seems very interesting. Also with our method, fistula closure could be performed as a simple and fast outpatient procedure and therefore does not add to the required hospitalization.

Dr. Tsapogas, we previously tried systemic fibrinolytic treatment with poor results. We have no experience with regional fibrinolysis or with fibrinolysis in conjunction with thrombectomy.

Dr. Raithel, it is well known that judging the results of venous surgery on the basis of clinical symptoms alone is insufficient. Our phlebographic findings, however, clearly demonstrate improved venous patency and valvular competence with this surgical procedure compared with anticoagulation alone, indicating that long-term clinical results will be improved also. Since rethrombosis routinely occurs following thrombectomy without an AV fistula, it is not surprising that the long-term results in Dr. Raithel's study were discouraging. However, it seems that your results were quite different from the results indicated by Dr. Nachbur. We are presently following up our patients with clinical and physiologic tests and, in a couple of years, Dr. Nachbur, we hope to learn if thrombectomy with AV fistula really prevents also the late postthrombotic sequelae.

PULMONARY EMBOLISM IN ACUTE ILIOFEMORAL VENOUS THROMBOSIS

G. Plate M.D., P. Ohlin M.D., Ph.D. and B. Eklöf M.D., Ph.D.

Departments of Surgery and Clinical Physiology, Central Hospital, Helsingborg,
Sweden

Correspondence to: Dr Gunnar Plate, Kirurgiska kliniken, Lasarettet, S-251 87
Helsingborg, Sweden

ABSTRACT

Serial perfusion lung scanning and chest radiography were used to study the incidence of pulmonary embolism in patients with acute iliofemoral venous thrombosis. The efficacy of conventional anticoagulation and surgical thrombectomy in controlling embolism and the risk of creating emboli during thrombectomy were also evaluated.

Lung scans obtained at admission in 49 patients were normal in 37 %, inconclusive in 18 % and positive for embolism in 45 % of the patients. Symptoms suggestive of embolism were present in only 24 % of the patients and correlated poorly to lung scans. Massive embolism was present in only 2 patients. Additional, usually asymptomatic, emboli developed within one month in 21 % of 29 patients treated conservatively with anticoagulation alone and in 20 % of 20 patients operated upon with acute thrombectomy combined with a temporary arteriovenous fistula and systemic anticoagulation. Only one conservatively treated patient required caval interruption.

Pulmonary embolism, usually of minor degree, is thus present in nearly every other patient with acute iliofemoral venous thrombosis. Anticoagulation alone or in conjunction with thrombectomy and arteriovenous fistula in most cases effectively prevents further embolization and the risk of creating additional emboli by the surgical procedure is insignificant.

Key words: Thrombosis, pelvic vein, pulmonary embolism, lung scanning, thrombectomy.

INTRODUCTION

The site of origin of pulmonary emboli has been much debated. Some authors claim that most emboli originate from the iliofemoral segment (1,2), whereas others maintain that the calf veins are a more common source for embolism (3,4). In cases of massive, life-threatening embolism, however, the emboli have usually been dislodged from thrombi located in the iliac or femoral veins (5-8).

The treatment of choice in acute iliofemoral venous thrombosis is controversial. Anticoagulation with heparin and vitamin K antagonists has been the standard treatment (9-12), but there are several reports suggesting that thrombolytic therapy or surgical thrombectomy better restores deep venous patency thereby preventing the late postthrombotic sequelae (13-19). The relative efficacy of these various treatments in controlling pulmonary embolism has not been thoroughly evaluated. Warnings have also been issued regarding risks of dislodging emboli during thrombolysis or thrombectomy (10,11,13,20, 21).

From July 1979 through June 1982 we performed a prospective randomized study comparing anticoagulation alone to acute thrombectomy combined with a temporary arteriovenous fistula and anticoagulation in the treatment of acute iliofemoral venous thrombosis. The clinical and phlebographic results after 6 months were superior with surgical treatment which has been presented in a previous report (19). The present study was performed to compare the relative efficacy of these regimens in controlling pulmonary embolism and to evaluate the risk of creating emboli during thrombectomy.

MATERIAL AND METHODS

Fifty-eight patients were admitted to the Central Hospital of Helsingborg, Sweden with acute iliofemoral venous thrombosis. Contrast phlebograms in all patients demonstrated deep venous thrombosis extending above the inguinal ligament but not into the vena cava. There were 25 men and 33 women with ages ranging from 15 to 80 (median 63) years. The thromboses affected the left leg in 44 cases and the right leg in 14 cases. Fourteen patients (24 %) complained of dyspnea, cough, chest pain or other symptoms that could be related to pulmonary embolism.

All patients were anticoagulated with intravenous heparin (Kabi, Sweden) for 5 - 7 days (bolus of 5 000 IU followed by a continuous infusion of 500 IU/kg/24 h adjusted to an activated partial thromboplastin time of 60 - 120 s) and oral dicumarol (Apekumarol, Ferrosan, Sweden) for at least 6 months. Twenty-seven patients were randomly allocated to acute venous thrombectomy combined with a temporary arteriovenous fistula created in the groin. The other 31 patients were treated conservatively with anticoagulation alone. Details of inclusions and exclusions, etiologies, medical and surgical procedures as well as clinical and phlebographic results after 6 months have been presented previously (19).

Perfusion lung scanning was performed at admission in 49 patients. Macroaggregated albumin (MAA) tagged with about 80 MBq of Tc-99m was injected intravenously. Using a scintillation camera, (Pho/Gamma LFOV, Searle, Des Plaines IL, USA) anterior, posterior, lateral (right and left) and posterior oblique (right and left) views of the lungs were obtained in 17 cases with the patient sitting. Posterior oblique views were replaced by anterior oblique views in thirty-two patients who could be examined only in the supine position. Lung scans were repeated in the sitting position after one week (48 patients) and again after one month (45 patients). All scans were supplemented with antero-posterior and lateral chest radiographies performed within 24 hours.

One of the authors (P.O.) has reviewed all scans without knowledge of treatment given or subsequent outcome. The scans were classified as normal (no perfusion defects), inconclusive (atypical defects or defects corresponding to radiographic

findings) or positive for pulmonary embolism (lobar or segmental perfusion defects without corresponding radiographic findings). The number of affected lung segments was estimated in patients with positive scans. The scintigraphic findings were correlated to site of the thrombus, presence of concomitant neoplasm and symptoms suggestive of embolism. Improvement or addition of new perfusion defects at one week and one month was evaluated in each treatment group. Chi square analysis was used for statistical comparisons.



Figure 1

Lung scan performed at admission in patient with an acute iliofemoral venous thrombosis but without symptoms of pulmonary embolism demonstrated perfusion defects in about 4 lung segments (left). Chest radiography was completely normal. At repeated lung scan after one month all previous perfusion defects had disappeared (right).

RESULTS

Lung scans at admission in 49 patients (Table 1) were normal in 18 cases (37 %). Nine patients (18 %) had inconclusive scans and 22 patients (45 %) had scans that were positive for embolism. In the latter group, the perfusion defects affected 1 - 2 lung segments in 9 patients, 3 - 5 segments in 11 patients and more than 5 segments in 2 patients.

Positive lung scans were obtained in 12 of 38 patients (32 %) with left-sided thrombi and in 6 of 11 patients (55 %) with right-sided thrombi (non-significant). Five of ten patients (50 %) with concomitant neoplasms had positive scans compared to 17 of 39 patients (45 %) without evidence of malignant disease.

There was a poor correlation between symptoms suggestive of embolism and positive lung scans. Sixteen non-symptomatic patients had positive scans (Fig. 1) and 3 patients with symptoms suggestive of embolism had normal lung scans. Both patients with massive embolism (more than 5 affected lung segments) had significant symptoms.

Lung scans at 1 week were obtained in 48 patients (Table 1). These scans revealed additional perfusion defects in 3 of 28 patients (11 %) treated conservatively and in 4 of 20 patients (20 %) operated upon with thrombectomy and arteriovenous fistula (non-significant). The additional perfusion defects were all minor and restricted to 1-2 lung segments and none of these patients developed any symptoms suggestive of embolism.

Lung scans at 1 month in 45 patients (Table 1) demonstrated that 3 conservatively treated patients had developed additional perfusion defects. One of these patients experienced recurrent symptomatic emboli despite adequate anticoagulation. She was operated upon with plication of the inferior vena cava using an Adams-DeWeese clip which prevented further embolization. The other two patients were asymptomatic, had only minor perfusion defects and received no additional treatment. In the surgical group no new perfusion defects were detected at one month.

The total incidence of new perfusion defects during the first month of treatment was 21 % (6 of 29 patients) in the conservative group and 20 % (4 of 20 patients) in the surgical group. At one month, the previous perfusion defects in 16 conservatively treated patients had disappeared in 9 (56 %) and improved in 4 patients (25 %). In the 13 operated patients with positive scans, the perfusion defects disappeared in 7 (54 %) and improved in 4 patients (31 %).

Table 1

PULMONARY EMBOLISM IN 49 PATIENTS WITH ACUTE ILIOFEMORAL
VENOUS THROMBOSIS

	<u>Conservative group</u>		<u>Surgical group</u>	
	patients	%	patients	%
Positive scans at admission	13/29	45	9/20	45
Additional perfusion defects after one week	3/28	11	4/20	20
Additional perfusion defects after one month	3/26	12	0/19	0

DISCUSSION

The present investigation was performed to study the incidence of pulmonary embolism in patients with acute iliofemoral venous thrombosis and to evaluate the influence of anticoagulation and surgical thrombectomy on further embolization. Perfusion lung scanning supplemented with chest radiography demonstrated typical perfusion defects in 45 % of the patients prior to treatment (Table 1). Only 24 % of the patients had symptoms suggestive of embolism and there was a poor correlation between symptoms and findings at lung scanning (Fig. 1). Emboli were slightly more frequent in patients with right-sided thrombi but not in patients with concomitant neoplasm. Anticoagulation alone or in combination with thrombectomy and arteriovenous fistula was followed by additional minor, asymptomatic emboli in about 20 % of the patients. In the surgical group a slightly greater incidence of embolism during the first week, perhaps due to intraoperative embolism, was compensated by a lower incidence during the remaining first month (Table 1). In both treatment groups, the one month lung scans demonstrated disappearance or improvement of previous perfusion defects in more than 80 % of the cases.

Pulmonary angiography is considered as the "golden standard" in the diagnosis of pulmonary embolism (22-25), but this invasive test is not suitable for screening (23). Perfusion lung scanning has been accredited a high sensitivity but a low specificity when compared to pulmonary angiography (23-28). Several authors have demonstrated that the specificity of perfusion lung scanning is greatly improved if ventilation scanning is added, but this was not possible in our institution (22, 26, 28). The combination of perfusion scanning with simultaneous chest radiography has proved nearly as reliable with a specificity of 73 - 100 % using the same criteria as ours (23-25,28). The performance of serial examinations, as in the present study, also improves the accuracy of the test (4, 28).

Pulmonary embolism has usually been reported in less than 25 % of patients admitted for iliofemoral venous thrombosis (29-33). Most likely, these numbers are too small, since objective screening for embolism is seldom performed. Two previous series of routine lung scanning demonstrated emboli in 40 - 50 % of patients with iliofemoral thrombosis and in 29 - 40 % in patients with calf vein

thrombosis (2,4). These reports corroborate the results of the present study (Table 1).

Anticoagulation alone offers sufficient protection from further pulmonary embolism in most cases of iliofemoral thrombosis (4,9,11,13, 14,21,33). This is supported by the results of the present study. Only one of our conservatively treated patients developed recurrent symptomatic embolism despite adequate anticoagulation. Occasional inability of anticoagulation treatment to control embolism has also been noted by others (2, 15, 16, 17, 20, 34).

During recent decades, thrombolytic treatment with streptokinase or urokinase has been used in the treatment of iliofemoral venous thrombosis. Some authors have found this treatment effective in controlling pulmonary embolism (14,15,17), whereas others indicate a slightly greater incidence of fatal embolism with thrombolytic treatment than with anticoagulation (13,20). It could be postulated that a partial thrombolysis could cause fragmentation and dislodgement of thrombotic segment.

Thrombectomy has been performed, mainly to prevent development of late postthrombotic sequelae, but this procedure carries a risk of dislodging emboli (11), and various adjunctive measures have therefore been taken to avoid this complication. Combination of thrombectomy with vein interruption has not proved to prevent embolism but increases the incidence of postthrombotic sequelae (12, 13, 18, 29, 35). Temporary occlusion of the vena cava by additional, "protective" balloon catheters was advocated by Fogarty (36), but fatal emboli have been reported despite the use of this extra device (13, 20, 34, 37). Purtscheller (38) has demonstrated that the intracaval pressure could be increased by positive-pressure ventilation or Valsalva manoeuvre during thrombectomy, but the clinical value of these manipulations remains to be proven. Adequate preoperative phlebography is probably of major importance in the avoidance of embolism. This allows preoperative detection of freely floating thrombi extending into the vena cava, which requires proximal control prior to thrombectomy (13, 36). Intraoperative fluoroscopy has also proved useful in assuring a complete vein clearance and in preventing intra- and postoperative embolism (39). In the present study thrombectomy was performed without any vein interruption but with the aid of pre-

operative phlebography, intraoperative fluoroscopy and positive-pressure ventilation resulting in a total lack of major embolic complications. Similar techniques for avoidance of embolism during thrombectomy have been used by others with equally favourable results (16, 18, 30, 32).

Mavor and Galloway (18) have demonstrated that an incomplete vein clearance during thrombectomy increases the incidence of rethrombosis and pulmonary embolism occurring postoperatively. There was no clearcut correlation between postoperative rethrombosis and embolism, however. In the present series no additional perfusion defects developed after the first postoperative week following thrombectomy combined with a temporary arteriovenous fistula. Since the arteriovenous fistula effectively prevented rethrombosis (19), it could be postulated that this was responsible for the low incidence of postoperative embolism as well.

In conclusion, the incidence of pulmonary embolism in acute iliofemoral venous thrombosis is around 50 % according to lung scans, which usually is underestimated when judged by symptoms alone. Anticoagulation treatment is effective in preventing further embolization in most cases. An adequate preoperative evaluation and a proper surgical technique allows thrombectomy to be performed safely without protective balloons or vein ligation.

REFERENCES

- 1 Bertelsen S. New aspects in pulmonary embolism. *Acta Chir Scand* 1971; 137:415-21.
- 2 Yao JST, Henkin RE, Bergan JJ. Venous thromboembolic disease. *Arch Surg* 1974; 109:664-70.
- 3 Browse NL, Lea Thomas M. Source of non-lethal pulmonary emboli. *Lancet* 1974; 1:258-9.
- 4 Kistner RL, Ball JJ, Nordyke RA, Freeman GC. Incidence of pulmonary embolism in the course of thrombophlebitis of the lower extremities. *Am J Surg* 1972; 124:169-76.
- 5 Havig Ö. Deep vein thrombosis and pulmonary embolism. *Acta Chir Scand Suppl* 1977; 478:42-7.
- 6 Linder F, Schmitz W, Encke A, Trede M, Storch HH. A study of 605 fatal pulmonary embolisms and two successful embolectomies. *Surg Gynecol Obstet* 1967; 125:82-6.
- 7 Mavor GE, Galloway JMD. The iliofemoral venous segment as a source of pulmonary emboli. *Lancet* 1967; 1:871-4.
- 8 Sevitt S, Gallagher N. Venous thrombosis and pulmonary embolism. A clinico-pathological study in injured and burned patients. *Br J Surg* 1961; 48:475-88.
- 9 Bauer G. Thrombosis. Early diagnosis and abortive treatment with heparin. *Lancet* 1946; 1:447-54.
- 10 Coon WW. Operative therapy of venous thromboembolism. *Modern Concepts of Cardiovascular Disease* 1974; 43:71-5.
- 11 Stephens GL. Current opinion on iliofemoral venous thrombectomy. *Am Surg* 1976; 42:108-15.
- 12 Young AE, Lea Thomas M, Browse NL. Comparison between sequelae of surgical and medical treatment of venous thromboembolism. *Br Med J* 1974; 4:127-30.
- 13 Denck H. Operative Therapie (Thrombektomie, Schirmfilter, Cavaligatur). *Langenbecks Arch Chir* 1977; 345:381-8.
- 14 Duckert F, Müller G, Nyman D, et al. Treatment of deep vein thrombosis with streptokinase. *Br Med J* 1975; 1:479-81.
- 15 Elliot MS, Immelman EJ, Jeffrey P, et al. A comparative randomized trial of heparin versus streptokinase in the treatment of acute proximal venous thrombosis: an interim report of a prospective trial. *Br J Surg* 1979; 66:838-43.

- 16 Fontaine R, Tuchmann L. The role of thrombectomy in deep venous thrombosis. *J Cardiovasc Surg* 1964; 5:298-312.
- 17 Kakkar VV, Flanc C, Howe CT, O'Shea M, Flute PT. Treatment of deep vein thrombosis. A trial of heparin, streptokinase, and arvin. *Br Med J* 1969; 1:806-10.
- 18 Mavor GE, Galloway JMD. Iliofemoral venous thrombosis. Pathological considerations and surgical management. *Br J Surg* 1969; 56:45-59.
- 19 Plate G, Einarsson E, Ohlin P, Jensen R, Qvarfordt P, Eklöf B. Thrombectomy with temporary arteriovenous fistula: The treatment of choice in acute iliofemoral venous thrombosis. *Journal of Vascular Surgery* 1984; 1:867-876.
- 20 Horsch S, Zehle A, Eisenhardt HJ, Landes T, Pichlmaier H. Chirurgische Behandlung der akuten Bein- und Beckenvenenthrombose. *Med Klin* 1979; 74:101-8.
- 21 Robertson BR, Nilsson IM, Nylander G. Thrombolytic effect of streptokinase as evaluated by phlebography of deep venous thrombi of the leg. *Acta Chir Scand* 1970; 136:174-80.
- 22 Cheely R, McCartney WH, Perry JR, et al. The role of noninvasive tests versus pulmonary angiography in the diagnosis of pulmonary embolism. *Am J Med* 1981; 70:17-22.
- 23 Kelley MJ, Elliott LP. The radiologic evaluation of the patient with suspected pulmonary thromboembolic disease. *Med Clin North Am.* 1974; 59:3-36.
- 24 Marini C, Ricco G, Palla A et al. Perfusion scintigraphy versus pulmonary arteriography in the diagnosis of pulmonary embolism. *J Nucl Med Allied Sci* 1978; 22:79-88.
- 25 Rosenow EC, Osmundson PJ, Brown ML. Pulmonary embolism. *Mayo Clin Proc* 1981; 56:161-78.
- 26 Bateman NT, Coakley J, Croft DN, Lyall RW. Ventilation-perfusion lung scans for pulmonary emboli. *Eur J Nucl Med* 1977; 2:201-3.
- 27 Bell WR, Simon TL. A comparative analysis of pulmonary perfusion scans with pulmonary angiograms. *Am Heart J* 1976; 92:700-6.
- 28 McCartney WH. Ventilation-perfusion lung scanning in pulmonary embolus. *Clin Nucl Med* 1981; 6:27-36.
- 29 Barner HB, Willman VL, Kaiser GC, Hanlon CR. Thrombectomy for iliofemoral venous thrombosis. *JAMA* 1969; 208:2442-6.
- 30 Lindhagen J, Haglund M, Haglund U, Holm J, Scherstén T. Ileofoemoral venous thrombectomy. *J Cardiovasc Surg* 1978; 19:319-27.

- 31 Mahorner H. Results of surgical operations for venous thrombosis. Surg Gynecol Obstet 1969; 129:66-70.
- 32 Röder OC, Lorentzen JE, Buchardt Hansen HJ. Acta Chir Scand 1984; 150:31-4.
- 33 Widmer LK, Madar G, Schmitt HE, Duckert F, Da Silva MA, Müller G. Heparin oder Thrombolyse in der Behandlung der tiefen Beinvenenthrombose. VASA 1974; 3:422-32.
- 34 Baumann G. Indikation, Technik und Ergebnisse der Thrombektomie. Chirurg 1976; 47:112-7.
- 35 Kistner RL, Sparkuhl MD. Surgery in acute and chronic venous disease. Surgery 1979; 85:31-43.
- 36 Fogarty TJ, Dennis D, Krippaehne WW. Surgical management of iliofemoral venous thrombosis. Am J Surg 1966; 112:211-6.
- 37 Andriopoulos A, Wirsing P, Bötticher R. Results of iliofemoral venous thrombectomy after acute thrombosis. Report on 165 cases. J Cardiovasc Surg 1982; 23:123-4.
- 38 Purtscheller W, May R. Surgery of the veins of the leg and pelvis. 1st ed. Stuttgart: Georg Thieme, 1979:76-81.
- 39 Mansfield AO, Carmichael JHE, Parry EW. Thrombectomy employing continuous radiological control. Br J Surg 1971; 58:119-23.

**ILIAC VEIN OBSTRUCTION
ASSOCIATED WITH ACUTE ILIOFEMORAL VENOTROMBOSIS
Results of early reconstruction using polytetrafluoroethylene grafts**

Gunnar Plate, Eibert Einarsson, Bo Eklöf, Ragnar Jensen, Per Ohlin.

Departments of Surgery, Radiology and Clinical Physiology,
County Hospital of Helsingborg, Sweden.

Correspondence to: Dr Gunnar Plate, Department of Surgery, Helsingborg County Hospital, S-251 87 Helsingborg, Sweden.

ABSTRACT

This retrospective study was performed to evaluate the results of iliac vein reconstructions when performed early after a secondary iliofemoral venous thrombosis. Seven patients undergoing acute thrombectomy combined with cross-femoral (4 cases) or ilio caval (3 cases) bypass procedures using polytetrafluoroethylene (PTFE) grafts were reviewed regarding clinical course, graft patency and venous physiology.

The clinical course was satisfactory in five patients but one patient died of postoperative complications and one patient underwent leg amputation after 20 months. Contrast and radionuclide phlebograms demonstrated that only one graft was still patent at 2 and 5 $\frac{1}{2}$ years postoperatively. Clinical symptoms and physiological parameters correlated poorly with graft patency demonstrating the necessity of using phlebography in evaluating patency rates after venous surgery.

Our results indicate that early venous reconstruction using PTFE grafts does not result in satisfactory long-term patency rates. Therefore this procedure rather is postponed and later considered only on those patients who develop severe postthrombotic sequelae. Further development of graft materials suitable for the venous system is required.

INTRODUCTION

A chronic iliac vein obstruction not seldom presents clinically as an acute iliofemoral venous thrombosis (3). In these cases surgical thrombectomy is often followed by early rethrombosis resulting in impaired emptying of blood from the lower extremity, ambulatory venous hypertension and subsequent leg swelling, venous ulcers or other postthrombotic sequelae (3, 10, 15, 18).

Palma & Esperon (16) and others (4, 9, 13) have demonstrated that iliac vein occlusions could be reconstructed with satisfactory clinical results using autogenous vein grafts. However, the long saphenous vein is often destroyed by previous thrombosis, wherefore autogenous graft material of adequate diameter not seldom is missing. A limited clinical experience with PTFE-grafts for venous reconstructions has been promising (5, 10), but long-term results including follow-up phlebography are missing.

Iliac vein reconstruction performed in the late stages after a secondary iliofemoral thrombosis is often compromised by postthrombotic fibrosis of the femoral veins (13). If the reconstruction instead is performed before the thrombosis has destroyed the veins, the chances of success ought to be better.

MATERIAL

This study includes seven patients, one male and six females, with ages ranging from 20 to 77 (mean 60) years. All were admitted for severe unilateral leg swelling with a duration of 1 - 4 days. Acute contrast phlebography revealed an iliofemoral thromboses in all cases with involvement of the peripheral venous system in all but one patient (case 5). An initial attempt at acute thrombectomy was performed in all patients, but reestablishment of venous continuity was not possible due to the associated chronic iliac vein obstructions, which prevented passage of the thrombectomy catheter into the vena cava. Presence of an associated obstruction of the iliac vein was confirmed by intraoperative fluoroscopy in 2 patients (cases 2, 4), by early post-thrombectomy phlebography in 3 patients (cases 2, 3, 6), and by direct surgical exploration in 5 patients (cases 1, 4, 5, 6, 7).

Venous reconstructions were performed in conjunction with the acute thrombectomy (cases 1, 3, 5, 7) or after 2 (cases 2, 4) and 49 days (case 6), respectively. Cross-femoral bypasses were established in four patients and three patients were reconstructed between the external iliac vein and the inferior vena cava using non-ringed PTFE-grafts in all cases (Table I). Autogenous reconstructions were not possible since the saphenous veins were previously removed or inadequate in size or quality. End-to-side anastomoses were used in all cases except in cases 5 and 6 who both had their iliac vein transected and the caudal anastomosis performed end-to-end. In six patients the graft was supported by a temporary arteriovenous fistula using the long saphenous vein or a separate PTFE-graft. The fistula was closed after 3 to 6 months. Antiplatelet (case 1) or anticoagulant therapy (cases 2 - 7) was given as long as the grafts were considered patent.

The etiology of the primary iliac obstruction was difficult to determine except in case 5, who had a liposarcoma that compressed the external iliac vein. It should be noted, that cases 1 and 2 simultaneously had diverticulitis of the sigmoid colon but without an obvious mechanical influence on the veins. Cases 4 and 6 had enlarged retroperitoneal lymph glands that could have been primary or secondary to the thrombophlebitis. Obstruction of the left common iliac vein caused by

compression of the overriding right common iliac artery was suspected in most cases since all thromboses were left-sided.

Table I

Sex, age, surgical procedure and medical prophylaxis in seven patients undergoing venous reconstruction with expanded polytetrafluoroethylene grafts.

<u>Case</u>	<u>Sex</u>	<u>Age</u>	<u>Reconstruction</u> *		<u>AV-fistula</u>	<u>Medical Treatment</u>
1	F	76	FFCO	8 mm	Autogenous	ASA + dipyridamole
2	F	65	FFCO	6 mm	Autogenous	Dicumarol
3	F	72	FFCO	6 mm	Autogenous	Dicumarol
4	F	20	FFCO	8 mm	Autogenous	Dicumarol
5	M	77	IC	10 mm	No	Dicumarol
6	F	46	IC	10 mm	PTFE	Dicumarol
7	F	61	IC	10 mm	Autogenous	Dicumarol

* FFCO = femoro-femoral crossover bypass

IC = ilio caval bypass

METHODS

Contrast phlebography as described by Gullmo (6) was performed at admission, in the early postoperative course (5 cases), at fistula closure (2 cases) and when graft thrombosis was suspected (2 cases). Follow-up phlebograms were obtained in cases 4 and 6 after 31 and 27 months, respectively.

Radionuclide phlebography was performed about 2 years postoperatively in cases 1, 2, 4 and 6 and was repeated after $5\frac{1}{2}$ years in case 6. Fifteen minutes after injection of a methylene-diphosphonate-kit (New England Nuclear), the erythrocytes were tagged in vivo with 500 MBq of $^{99}\text{Tc}^{\text{m}}$ -pertechnetate. First passage and equilibrium images of the iliac vessels were obtained using a scintillation camera (LFOV, Searle) with a microprocessor-based computer (Scintiview, Searle).

Venous plethysmography was performed as described by Hallböök & Göthlin (7). Emptying capacities less than $40\text{ ml} \times \text{min}^{-1} \times (100\text{ g})^{-1}$ were considered subnormal. An impaired late venous outflow was looked for, since this has been described in acute iliac vein thrombosis (19).

Foot volumetry was carried out according to Norgren (14). The EVrel (relative expelled volume) is expressed as the reduction of foot volume after knee bendings related to foot volume at rest, thus estimating the muscle pump function. The Q/EVrel expresses refilling flow after exercise in relation to EVrel, indicating the degree of venous reflux.

Ambulatory foot vein pressure. Butterfly needles (0.6 mm outside diameter) were inserted into dorsal foot veins and connected to a pressure transducer (Siemens Elema, Sweden). The pressure reduction during heel raising 60 and 120 min^{-1} was calculated. In healthy individuals the maximum pressure reduction should exceed 50 mmHg (11).

RESULTS

The early postoperative period was uncomplicated with a rapid decrease of leg swelling in all cases. Two patients (cases 1 and 7) developed transient lymphorrhea from the groin wound. Case 3 was complicated by septicemia which necessitated removal of the graft and closure of the arteriovenous fistula after 1 week. She expired from myocardial infarction with cardiac failure after a month. Cases 1 and 5 experienced sudden leg swelling when their grafts occluded after 2 and 11 months, respectively. One of these patients (case 5) developed an arterial insufficiency after 20 months and his leg was amputated above the knee. This patient later expired due to metastases from his liposarcoma. The 5 surviving patients suffered only slight leg swelling at follow-up two to three years post-operatively (Table II).

Contrast and radionuclide phlebograms are summarized in Table II. Phlebograms obtained early after the venous reconstruction in 5 patients demonstrated 1 occluded (case 3) and 4 patent grafts (cases 4, 5, 6, 7). Phlebography performed at fistula closure in 2 patients revealed one occluded (case 7) and one patent graft (case 2). Two additional grafts (cases 1, 5) occluded within a year and two were occluded at 26 (case 2) and 31 months (case 4) postoperatively. In case 6 the iliocaval bypass graft is still patent after 5 $\frac{1}{2}$ years, although contrast and radionuclide phlebography have demonstrated a progressive stenosis at the lower anastomosis (Fig. 1). In all cases where the iliac vein had not been transected (cases 1, 2, 4 and 7) the caudal segment of the iliac vein was still patent and the collaterals were abundant.

Venous plethysmography performed in four patients after their grafts had occluded revealed a reduced initial outflow only in one case (Table II). It was also subnormal in the patient with a patent graft (case 6). No marked late retardation of the venous outflow was observed in patients with a normal initial venous outflow.

Foot volumetry was performed in four patients (Table II). The examination was normal in case 7, who had an occluded graft. In the other patients, one of which (case 6) had a patent graft, the EVrel was decreased and the Q/EVrel increased.

The ambulatory foot vein pressure was examined in three patients (Table II). The maximum pressure reduction was less than 50 mm Hg in the patient with a patent graft (case 6) but normal in two patients with occluded grafts (cases 4 and 7).

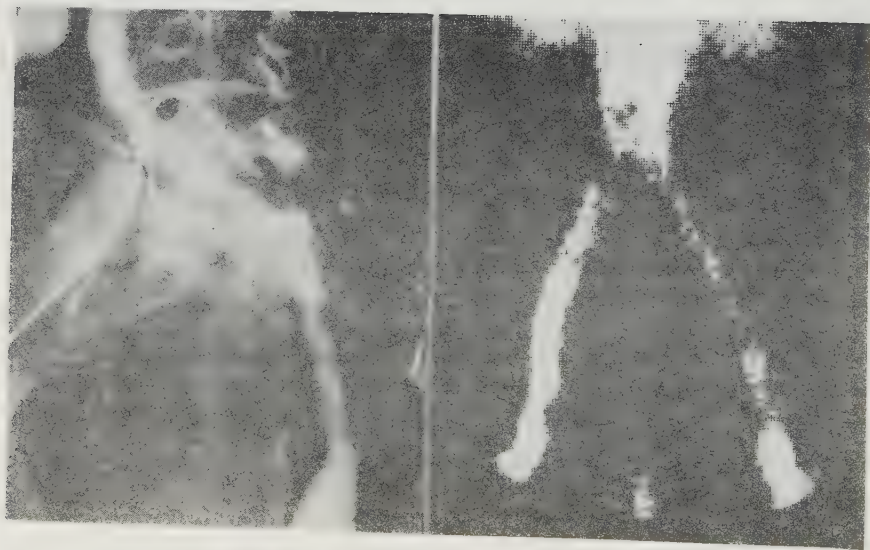


Figure 1

Case 6: Angiography via the arteriovenous fistula one month after venous reconstruction demonstrated a patent ilio caval PTFE-graft (left). At follow-up radionuclide (right) and ascending contrast phlebography after 27 months the graft was still patent but a stenosis had developed at the caudal anastomosis.

TABLE II

Contrast and radionuclide phlebograms, late sequelae and physiological parameters at follow-up after 1 - 3 years in seven patients undergoing reconstruction for iliac vein obstruction.

Case	Contrast and Radionuclide Phlebograms Graft Occlusion (months)	Collaterals	Late Sequelae	Venous Plethysmography (mlxmin ⁻¹ x 100 g ⁻¹)	Foot Volumetry EVrel (ml/100 ml)	Q/VE _{rel} (min ⁻¹)	Ambulatory Foot Vein Pressure Reduction (mmHg)
1	2	Good	Slight swelling	25	--	--	--
2	3 - 26	Good	Slight swelling	53	0.5	13.2	--
3	0	--	Expired	--	--	--	--
4	21 - 31	Good	Slight swelling	67	0.4	3.5	58
5	11	Bad	Amputation Expired	--	--	--	--
6	Patent	Bad	Slight swelling	21	0.5	3.2	35
7	0 - 6	Good	Slight swelling	72	0.8	1.4	78

DISCUSSION

The purpose of this study was to evaluate the results of early reconstruction of chronic iliac vein obstructions in cases presenting with acute iliofemoral venous thrombosis. The great number of intermediate-late graft occlusions recorded in the present study could be explained by the use of a synthetic and thereby thrombogenic graft material. Autogenous veins of adequate diameter and quality were not available. It should be noted that despite the great number of graft occlusions, all five surviving patients only had minimal leg swelling 1 - 3 years postoperatively.

Progressive stenosis at the suture lines is another cause of late graft occlusions in the venous system (12). In the present study anastomotic strictures were noted at phlebography in cases 5 and 6 (Fig. 1). Refinement of the surgical technique, use of fine suture material and external ring support of the anastomosis were suggested by Kunlin & Kunlin (12) as means of avoiding this complication.

The present study demonstrated a discrepancy in late clinical results and graft patency (Table II). This could be related to the development of an adequate collateral circulation in patients with occluded venous prostheses. In five cases (1 - 4, 7) on whom the iliac vein initially was not transected, the caudal vein segment was still patent, the collaterals were abundant and leg swelling was minimal. It is possible that the arteriovenous fistula and the venous bypass could have contributed to preservation of venous patency and to development of collaterals in these patients (2, 5, 17). This theory implies that the iliac vein should not be transected and the anastomoses should be performed end-to-side.

By the physiological examinations used in this study it was not possible to state the patency of the grafts (Table II). This is not surprising since at least foot volumetry and ambulatory foot vein pressure measurement mainly reflect peripheral venous disease. Venous plethysmography has been reported successful in detecting acute iliac vein obstructions (19). Our results indicate that plethysmograms obtained after iliac vein reconstructions reflect not only graft patency but also adequacy of the collateral circulation.

Contrast phlebography provides the only clearcut proof of the patency of venous grafts (2, 13). Reports of successful venous reconstructions, where phlebography has not been used in the follow-up therefore should be regarded with scepticism. Warnings have been issued regarding induction of venous thrombosis by the contrast material injected (1). Repeated contrast phlebographies in patients with previous deep venous thrombosis probably is even more hazardous. Therefore, we tried radionuclide phlebography for evaluation of graft patency. This can be done in two ways. If radioactive macroaggregates of albumin (MAA) are injected into a vein on the dorsum of the foot, the iliofemoral segment usually could be well visualized (8). Puncture of a foot vein in a postthrombotic leg sometimes is painful or even impossible. The technique described in this study with in-vivo erythrocyte tagging and injection of a radioactive material via a cubital vein is almost painless and technically easier. If this examination initially is compared with a contrast phlebogram, repeated studies probably provide reliable information on iliac vein or graft patency.

In conclusion, early reconstruction of a chronic iliac vein obstruction using PTFE-grafts does not provide better long-term graft patency rates than previously reported results of reconstruction in the late postthrombotic stages. Presently it seems preferable to postpone the reconstructive procedure to be performed only in those patients who develop severe late postthrombotic sequelae on the basis of a persistent venous occlusion. Future development of graft materials more suitable for the venous system and refinement of surgical techniques hopefully could improve our results of venous reconstructive surgery.

REFERENCES

- 1 Albrechtsson, U. & Olsson, C.-G. 1976. Thrombotic side-effects of lower-limb phlebography. *Lancet* 1, 723.
- 2 Brunner, U. 1979. Surgery of acute femoroiliac phlebothrombosis. In *Surgery of the veins of the leg and pelvis*. (ed. R May) pp 105-133, Georg Thieme Publ, Stuttgart.
- 3 Cockett, F.B., Lea Thomas, M., Negus, D. 1967. Iliac vein compression. Its relation to iliofemoral thrombosis and the postthrombotic syndrome. *Br J Med* 2,14.
- 4 Dale, W.A. 1966. Chronic iliofemoral venous occlusion including 7 cases of cross-over vein grafting. *Surgery* 59,117.
- 5 Gruss, J.D., Bartels, D., Tsafandakis, E., Schlechtweg, B., Machado, J.L. 1981. Blood vessel prostheses in the Palma operation. In *Pelvic and abdominal veins* (ed. R. May & J. Weber) pp 241-248, Excerpta Medica, Amsterdam.
- 6 Gullmo, Å. 1955. On the technique of phlebography of the lower limb. *Acta Radiol* 46,603.
- 7 Hallböök, T. & Göthlin, J. 1971. Strain gauge plethysmography and phlebography in diagnosis of deep venous thrombosis. *Acta Chir Scand* 137,37.
- 8 Hayt, D.B., Blatt, C.J., Freeman, L.M. 1977. Radionuclide venography; Its place as a modality for the investigation of thromboembolic phenomena. *Sem Nucl Med* 7, 263.
- 9 Husni, E.A. 1971. Venous reconstruction in postphlebitic disease. *Circulation Suppl.* 18-19,147.
- 10 Hutschenreiter, S., Vollmar, J., Leoprecht, H., Abendschein, A., Rödl, W. 1979. Rekonstruktive Eingriffe am Venensystem -Spätergebnisse unter kritischen Bewertung funktioneller und gefäßmorphologischer Kriterien. *Chirurg* 50,555.
- 11 Kriessman, A. & May, R. 1978. Empfehlungen zur Standardisierung und praktischen Anwendung der peripheren Venendruckmessung. In *Periphere Venendruckmessung*. (eds. R. May & A. Kriessman) pp. 177-179, Georg Thieme Verlag, Stuttgart.
- 12 Kunlin, J. & Kunlin, A. 1979. Experimental venous surgery. In *Surgery of the veins of the leg and pelvis*. (ed R. May) pp 37-75, Georg Thieme Publ, Stuttgart.
- 13 May, R. & De Weese, J.A. 1979. Surgery of the pelvic veins. In *Surgery of the veins of the leg and pelvis* (ed. R. May) pp 158-184, Georg Thieme Publ., Stuttgart.

- 14 Norgren, L. 1974. Functional evaluation of chronic venous insufficiency by foot volumetry. *Acta Chir Scand Suppl* 444.
- 15 O'Donnell, T.F., Browse, N.L., Burnand, K.G., Lea Thomas, M. 1977. The socioeconomic effects of an iliofemoral venous thrombosis. *J Surg Res* 22,483.
- 16 Palma, E.C. & Esperon, R. 1960. Vein transplants and graft in the surgical treatment of the postphlebitic syndrome. *J Cardiovasc Surg* 1,94.
- 17 Vollmar, J., Loeprecht, H., Hutschenreiter, S. 1978. Rekonstruktive Eingriffe am Venensystem. *Chirurg* 49,296.
- 18 Weber, J., Wirth, W., Brunner, U. 1973. Die frische Iliofemoralvenenthrombose. *Fortschr Röntgenstr* 119,666.
- 19 Zetterquist, S., Eriksson, K., Volpe, U. 1975. The clinical significance of biphasic venous emptying curves from the lower limbs in venous occlusion plethysmography. *Scand J Clin Lab Invest* 35,497.

Overcoming failure of venous vascular prostheses

Gunnar Plate, M.D.,* Larry H. Hollier, M.D., Peter Gloviczki, M.D.,
Mrinal K. Dewanjee, Ph.D., and Michael P. Kaye, M.D., Rochester, Minn.

Thrombogenicity of graft material, low velocity of blood flow, and wall collapsibility have been cited as the main factors responsible for the high occlusion rate of vascular prostheses placed in the venous system. This study was performed to analyze the effects of measures taken to overcome each of these factors. The thrombogenicity of expanded polytetrafluoroethylene (ePTFE) was evaluated by determination of the 3-hour deposition of radionuclide-labeled platelets and fibrin on grafts placed in the infrarenal vena cava of 18 dogs. Wetting the prosthesis with heparin before implantation significantly decreased platelet deposition at the cranial anastomosis ($p < 0.025$) and on the graft surface ($p < 0.01$), whereas the decrease of fibrin deposition was not statistically significant. The effects of flow velocity and graft support were studied in 44 dogs subjected to ilio caval bypass. The results of these studies demonstrated that a flow-increasing arteriovenous fistula was necessary to maintain patency of ePTFE grafts ($p < 0.01$) but did not enhance patency of autogenous vein grafts. External ring support of ePTFE grafts did not significantly improve early patency. Decreasing thrombogenicity by wetting the grafts with heparin and increasing the blood flow by constructing an arteriovenous fistula helps in overcoming failure of venous vascular prostheses.

From the Department of Surgery and the Section of Diagnostic Nuclear Medicine, Mayo Clinic and Mayo Foundation, Rochester, Minn.

PHYSIOLOGIC STUDIES HAVE shown that both adequate arterial blood supply and sufficient venous drainage are required to maintain circulation of the lower extremities.^{19,39} These laboratory studies are supported by clinical experience from the Korean and Vietnam conflicts in which concomitant venous injury was noted in 62% to 70% of the casualties who had major arterial injuries.^{21,42} It was further noted that the incidence of limb loss and late sequelae could be decreased if not only arterial, but also venous continuity was reestablished. Evidence also exists that primary venous obstruction can jeopardize the peripheral circulation. Amputation rates as high as 30% have been reported in phlegmasia cerulea dolens caused by occlusion of the major outflow from the lower limb,⁴¹ and acute iliofemoral thrombosis can lead to late amputation necessi-

tated by chronic ulcerations and pain.³ Compression of the left common iliac vein between the overlying right common iliac artery and the spine is the usual underlying cause of obstruction of the major venous outflow of the lower extremities.^{3,5,45} This so-called "iliac compression syndrome" is often complicated by thrombosis of the iliofemoral segment, which further decreases the venous outflow by occluding important collaterals.³

Although the above conditions demonstrate the need for venous reconstruction, such surgery has evolved more slowly than its arterial counterpart. It was not until the early 1960s that the first success in patients with iliac compression syndrome was reported by Palma and Esperon.³³ Subsequently, using the techniques of Palma and Esperon, Dale⁶ and Husni²² have reported success in 60% to 80% of patients with venous reconstruction. Unfortunately, autogenous veins are not always available. In reconstruction of postphlebotic cases, for example, the saphenous veins that otherwise could have been used as vascular conduits are often involved in the phlebotic process or have been surgically removed because of incompetence.¹⁴ Autogenous graft

This work was supported in part by the Rappaport Clinician-Investigator Fellowship Program

Accepted for publication Oct. 11, 1983.

Reprint requests: Larry H. Hollier, M.D., Department of Surgery, Mayo Clinic, Rochester, MN 55905.

*Winner, Sigvaris Award on Venous Disease, 1983

Table I. Graft material and use of AV fistulas in 44 dogs with ilio caval venous reconstruction

Group	No. of dogs	Graft material	AV fistula
I	10	Autogenous vein	No
II	10	Autogenous vein	Yes
III	6	Ringed ePTFE	No
IV	10	Ringed ePTFE	Yes
V	8	Nonringed ePTFE	Yes

material of adequate diameter is also not available for reconstruction of the major veins. A prosthesis suitable for use in the venous system is therefore required.

Experimental experience with venous vascular prostheses has been discouraging.^{6, 15, 18, 37} All synthetic grafts are more or less thrombogenic.* The results with expanded polytetrafluoroethylene (ePTFE) grafts have been promising†; this has been suggested to be due to lower thrombogenicity as a result of its smooth, hydrophobic and negatively charged inner surface.^{35, 45} In attempts to decrease thrombogenicity, incorporation of anticoagulants and antiplatelet drugs into the graft wall has been tried experimentally‡ with some success. The place of these procedures in clinical practice is not yet established. To increase blood flow and improve patency of venous grafts, in 1953 Kunlin⁴⁴ introduced the use of a temporary arteriovenous (AV) fistula. Despite some contradiction, experimental reports are usually supportive of the beneficial effects of this procedure.§ Since collapse and compression of grafts have also been implicated as causes of graft failure in the low-pressure venous system,^{1, 4, 37} support of the graft wall has been tried as a means of avoiding collapse of venous prostheses.¶ Further studies have yet to provide evidence that such support improves graft patency.

Since there appear to be three major factors contributing to graft failure, this study was designed to evaluate each factor and determine its contribution to early occlusion of ePTFE grafts used as venous substitutes.

MATERIALS AND METHODS

Part I: Studies on graft thrombogenicity. Eighteen mongrel dogs weighing 18 to 27 kg (mean 22.4 kg) were anesthetized, and the vena cava was exposed

through a midline abdominal incision. After systemic heparinization (100 U/kg), 3 cm of the infrarenal vena cava was replaced with 5 cm of an ePTFE graft (Gore-Tex; externally ring-supported, 30 μ pore size, 10 mm inner diameter) with continuous 6-0 nonabsorbable (Prolene) sutures. Two groups of animals were studied. In the control group (10 dogs) the grafts were implanted as provided by the manufacturer, and in the treated group (eight dogs) the grafts were perfused with sodium heparin before implantation, as described by Takamatsu.⁴³ For this purpose, the grafts were placed in a glass syringe containing heparin sodium (1000 U/ml), and the piston was repeatedly withdrawn and pressed against a sealed outflow to exchange the air within the pores of the ePTFE with heparin.

To determine the acute platelet and fibrin deposition, autogenous platelets labeled with indium-111 tropolone and heterologous fibrinogen labeled with iodine-125 were administered intravenously 15 minutes before declamping. The labeling was performed as described by Dewanjee et al.⁷ and Fraker and Speck.¹² Three hours later blood samples were obtained for determination of platelet counts and radioactivity in blood. The graft with the adjacent vena cava was removed. After gentle rinsing with 40 ml of isotonic saline solution and cleaning of the external surface, the graft was cut into five sections: the proximal and distal anastomotic areas including 2 mm of vena cava and 5 mm of graft and three equally divided intervening graft segments. The surface area of each segment was determined and the radioactivity measured in a γ -well counter. With the knowledge of the number of circulating platelets, the concentration of fibrinogen, and the radioactivity in blood, the number of platelets and amount of fibrinogen/fibrin counts per minute could be calculated. With the radioactivity of each graft segment, the number of platelets and amounts of fibrin deposited per surface area could also be determined. The mean $\pm$ SD of the number of platelets and micrograms of fibrin per square millimeter were calculated for each segment. Platelet and fibrin deposition on the intervening segments of non-clotted grafts were analyzed with the Student *t* test. The numerical value for grafts with major clot formation was not used, but the incidence of clotted grafts in the two groups was compared by χ^2 analysis.

Part II: Studies on flow velocity and wall collapsibility. Forty-four mongrel dogs weighing 13 to 27 kg (mean 18.7 kg) were subjected to ilio caval venous reconstruction. The dogs were anesthetized with intravenous pentobarbital, intubated, and prepared in a

*References 6, 15, 18, 29, 37.

†References 11, 14, 38, 40, 45, 46.

‡References 29, 31, 32, 43.

§References 13, 17, 20, 23, 27, 30, 36, 47.

¶References 9, 10, 17, 36, 44.

sterile fashion. Gentamicin sulfate (80 mg, administered intravenously) and penicillin G benzathine (1,200,000 U, administered intramuscularly) were administered as single doses immediately before the operation. The abdomen was entered through a mid-line incision and the vena cava and left iliac vein were dissected free. Systemic heparinization (300 U/kg) was instituted and the left common iliac and hypogastric veins were ligated and transected.

The dogs were divided into five groups that used autogenous vein and ringed and nonringed ePTFE grafts with and without a fistula (Table I). The AV fistula was constructed immediately before the implantation of the graft by performing an 8 mm long side-to-side anastomosis between the left superficial femoral artery and vein with a continuous 7-0 Prolene suture. Autogenous vein grafts were harvested with meticulous technique from the external jugular vein and implanted immediately. ePTFE grafts with and without external ring support (Gore-Tex, 30 μ pore size, 8 mm inside diameter) were provided by W. L. Gore & Associates, Inc. All of the ePTFE prostheses were wetted out with heparin, as described in Part I.

Twelve centimeter segments of the grafts were implanted between the external iliac vein (end-to-end) and the infrarenal vena cava (end-to-side) with continuous 6-0 Prolene sutures (Fig. 1). All grafts were placed posterior to the sigmoid colon and left adnexa. Blood flow through the grafts was measured in 21 dogs with a square wave electromagnetic flowmeter (FM 501, Carolina Medical Electronics, Inc.). In cases in which an ePTFE graft had been implanted, the flow was measured in the vena cava proximal to the anastomosis while occluding the cava caudal to the anastomosis. Finally, the wounds were closed in three anatomic layers.

Closure of the fistula was performed under barbiturate anesthesia 1 month after the initial procedure. The femoral artery was exposed and a continuous mattress suture of 5-0 Prolene was placed through the fistula. Disappearance of the thrill from the fistula was checked in all cases. In six dogs (three in each of groups II and IV) the fistula had reopened at 3 months and was therefore reclosed by ligation of the superficial femoral artery immediately proximal and distal to the fistula. Persistence of pulses distally indicated an adequate collateral circulation.

Phlebography was performed under pentobarbital anesthesia after 1 week and at 1, 3, and 6 months after operation. A 16-gauge catheter was introduced into the left lateral saphenous vein. With use of a power injector, 32 ml of a water-soluble contrast medium



Fig. 1. Iliocaval reconstruction with ringed ePTFE graft and distal AV fistula.

(Renografin-76, Squibb) was infused into the venous system with visualization of dye recorded on videotape and single plane spot films. If the graft was not visualized, the dog was killed and the graft removed for confirmation of occlusion and morphologic examination. The animals in groups I to IV have now been followed for 6 months, whereas only 3-months results are available in group V. The patency rates were calculated at each time interval. The influence of an AV fistula on early patency of ePTFE and autogenous vein grafts was obtained by a comparison of the results of group I to II and group III to IV. The effect of external ring support of ePTFE grafts was determined by comparison of group IV to V. Chi square analysis was used for statistical evaluation of patency rates.

Animals with patent grafts were killed 6 months

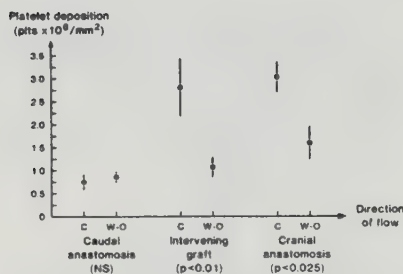


Fig. 2. Deposition of indium-111-labeled platelets on non-clotted ePTFE grafts 3 hours after implantation in the infrarenal vena cava of 12 dogs. (C, Controls; W-O, grafts wetted out with heparin.)

after operation. Two hours after an intravenous injection of 2 ml/kg of a 0.5% solution of Evans blue, the dogs were anesthetized with pentobarbital, the abdomen was explored, and the graft was dissected. After heparinization, the graft was perfusion fixed with buffered glutaraldehyde and formalin (Trump's solution) at a pressure of 10 cm of water and then harvested. The grafts were opened longitudinally and photographed, and selected specimens were processed for light and electron microscopy.

RESULTS

Part I. Five of 10 control grafts and one of eight heparin-perfused ePTFE grafts were clotted when removed 3 hours after implantation. Although clotting appeared more frequent and of greater degree in the control group, the difference was not statistically significant ($0.05 < p < 0.1$). When the deposition of platelets on the clotted grafts was determined, it was approximately five times greater than on nonclotted grafts, and accordingly these values were not used in comparing the two groups.

On nonclotted grafts the platelet deposition on the intervening graft, excluding the anastomosis, was greater in the cranial segments. Since these differences in distribution did not reach statistical significance, the numbers were pooled for the whole of the intervening graft. These data are presented in Fig. 2. Platelet deposition on the caudal anastomosis of control grafts was significantly less than on the cranial anastomosis ($p < 0.001$) and on the intervening graft ($p < 0.01$). Wetting out the graft with heparin decreased platelet deposition significantly, both on the cranial anastomosis ($p < 0.025$) and on the intervening graft ($p < 0.01$).

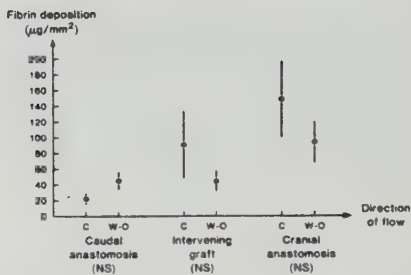


Fig. 3. Deposition of ^{125}I -labeled fibrin on nonclotted ePTFE grafts as in Fig. 2.

The deposition of fibrin (Fig. 3), as for platelets, was pooled for the whole intervening graft. Fibrin deposition of control grafts was also less pronounced on the caudal anastomosis than on the cranial anastomosis ($p < 0.025$) and on the intervening graft segment (not significant). No significant difference in deposition was found, however, when comparing the control and the wetted-out grafts.

Part II. Blood flow through the ilio caval grafts was 49 ± 18 ml/min (mean $\pm$ SD) in nine dogs without an AV fistula and 832 ± 378 ml/min in 12 dogs with an AV fistula. This difference was statistically significant ($p < 0.01$). The AV fistula thus created a seventeenfold increase in blood flow through the graft. There was no significant difference in blood flow between autogenous and prosthetic grafts. The influence of the AV fistula on graft patency is presented in Fig. 4. Three of 10 autogenous ilio caval reconstructions performed without an AV fistula (group I) occluded within 1 week, but the other seven grafts remained patent for 6 months. The same results were obtained if an AV fistula had been added (group II), although two of these animals died of unrelated causes after 2 and 3 months, respectively. No dogs with autogenous vein grafts experienced graft occlusion after the first postoperative week. All six ePTFE grafts implanted without an AV fistula (group III) were occluded after 1 week (Fig 5). Seven of 10 ePTFE grafts were patent at 1 month when supported by an AV fistula. Of these seven grafts patent at 1 month, one was occluded at the 3-month study. The other six grafts in this group remained patent at 6 months (Fig 5). With the use of nonringed ePTFE grafts and an AV fistula (group V), four of eight grafts were patent at 1 month after operation. At the 3-month study one more graft had occluded, leaving only three of eight grafts still patent.

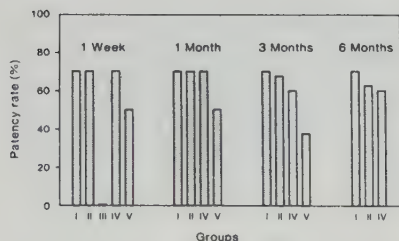


Fig. 4. Influence of AV fistula on patency at 1 week, 1 month, 3 months, and 6 months after ilio caval venous reconstruction. Group I: autogenous vein graft (n = 10); group II: autogenous vein graft and AV fistula (n = 10); group III: ringed ePTFE graft (n = 6); group IV: ringed ePTFE graft and AV fistula (n = 10); group V: nonringed ePTFE graft and AV fistula (n = 8).

An unexpected finding was noted in our postmortem studies. Five of the 28 animals with an AV fistula that underwent operation (groups II, IV, and V) died within 1 week. Autopsy revealed graft thrombosis with pulmonary embolism as the probable cause of death in four of these animals. None of the dogs without an AV fistula that underwent operation died of pulmonary embolism.

Thus, as described in Fig. 4, the patency rates for autogenous vein grafts were the same without an AV fistula (group I) as with an AV fistula (group II). The AV fistula did, however, improve the patency of ePTFE grafts (groups III and IV) dramatically ($p < 0.01$). The patency of nonringed ePTFE grafts (group V) was less, but not significantly different from the ringed ePTFE grafts (group IV). With an AV fistula, the results with ePTFE grafts (group IV) 6 months after operation were not statistically different from autogenous vein grafts (groups I and II). It should be noted that all of the ePTFE grafts used in this part of the experiment were wetted out with heparin.

Autogenous vein grafts harvested at 6 months all had a nice, smooth, light blue inner surface, which was verified by light and electron microscopy to be composed of endothelium. Four of the six ePTFE grafts patent at 6 months, however, had significant mural thrombus formation, mainly located in the cranial third of the graft. Other areas of the graft had a thin pseudointima with a smooth surface, including the areas of anastomotic ingrowth as well as 10% to 40% of the middle portion of the graft. Light microscopy, as well as scanning and transmission electron microscopy, from these areas showed a single cellular layer with the appearance of endothelial cells.

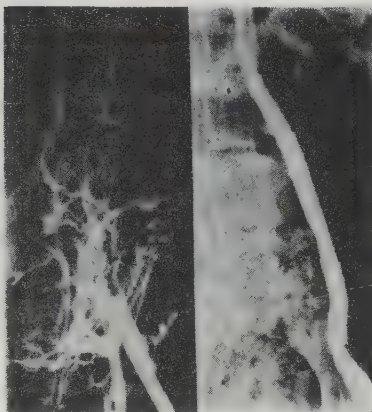


Fig. 5. Phlebograms show an occluded ePTFE graft 1 week after implantation without an AV fistula (left) and a patent ePTFE graft 6 months after ilio caval reconstruction supported by an AV fistula (right).

DISCUSSION

The present study was performed to evaluate the contributions of graft thrombogenicity, low blood flow velocity, and graft wall collapsibility on early occlusion of venous vascular prostheses. The effect of measures taken to avoid each of these factors was also analyzed. Since ePTFE grafts have provided the best clinical results in the venous system, these prostheses were selected for further study. Thrombogenicity was studied on grafts placed in the infrarenal vena cava, where most previous experience is available.* For studies of the influence of blood flow velocity and graft collapsibility, reconstruction with relatively long ilio caval grafts was used to simulate the clinical situation^{3,33,34,45} and to test graft patency under relatively unfavorable conditions.^{25,37}

The findings of this study revealed that the acute deposition of platelets and fibrin on ePTFE grafts placed in the venous system was mainly localized to the graft surface and to the cranial anastomosis. Wetting out of the graft with heparin significantly decreased platelet deposition at both these locations (Fig. 2), whereas fibrin deposition was not affected (Fig. 3). Major clot formation occurred more often in control grafts than in wetted-out grafts, but the number of observations was too small to provide a significant

difference. The flow-increasing AV fistula did not improve patency of ilioacaval autogenous vein grafts but was mandatory to maintain patency of ePTFE grafts. External ring support of ePTFE grafts did not provide significant improvement of early patency, but the observation time is still shorter for the nonringed grafts. The patency rate with heparin-perfused ePTFE grafts supported with an AV fistula was comparable to the patency of autogenous vein grafts.

Our results thus indicate that graft thrombogenicity and low velocity of blood flow are the main factors responsible for graft failure, whereas graft wall collapsibility seems to be of lesser importance. Wetting out with heparin decreases thrombogenicity, and a flow-increasing AV fistula improves patency of ePTFE grafts.

Kunlin and Kunlin²⁵ and others^{17,37,47} have reported that transplanted grafts are subjected to a progressive stenosis at the suture line. The marked deposition of platelets and fibrin noted at the cranial anastomosis implies that both platelets and fibrin could play a major role in the development of these stenoses. Our wetting-out procedure decreased the deposition of platelets at the cranial anastomosis. Previous experiments in this laboratory²⁸ have shown that systemic antiplatelet treatment also decreases the anastomotic deposition of both platelets and fibrin. These studies thus indicate that local application or systemic administration of antiplatelet and anticoagulant drugs may be helpful in avoiding late graft occlusion caused by stenosis at the suture lines.

Madras et al.²⁹ have shown that complete wetting out of ePTFE grafts decreased the *in vitro* preactivation of blood. The present study provided evidence that the *in vivo* thrombogenicity also was improved by this procedure. Whether this was due to the pharmacologic effects of the heparin incorporated into the graft wall or to the removal of air from the graft-blood interface has not been elucidated. The durability of these effects is, of course, debatable, but Takamatsu⁴³ has shown that heparin could be dissolved from the graft material up to 1 month after the wetting-out procedure. Promising results with more sophisticated binding and release of heparin have been reported,^{31,32} but clinical experience is still limited. Experiments with systemic administration of antiplatelet drugs performed in this laboratory^{13,28} showed a decrease of platelet deposition to a similar level as accomplished in the present study with the wetting-out procedure. Clinical evidence of long-term benefit with systemic antiplatelet treatment is also lacking.

In contrast to the results of our study, Scheinin³⁶

reported that an AV fistula improves patency of autogenous vein grafts. He replaced 5 cm segments of the infrarenal vena cava with autogenous veins harvested from the external jugular vein. The patency rates increased from 20% to 61% with the addition of an AV fistula. The diameter of the autogenous grafts used must inevitably have been less than the diameter of the vein replaced. The hemodynamic effects of graft size discrepancy in the venous system are not well elucidated. A decrease in luminal diameter could theoretically provide an increase in blood flow velocity if the total blood flow is constant. It is, however, uncertain that the total flow through the graft segment is constant, since the propulsive pressure usually is low and collateral pathways are abundant.²⁵ Most authors agree that the ideal graft should be isodiametric to avoid turbulence in the blood stream.^{25,37} Johnson and Eiseman²³ and Levin et al.²⁷ also found an AV fistula to be beneficial for autogenous reconstruction. They placed the grafts in the canine femoral vein where the blood flow velocity is lower and the occlusion rate is higher.²⁴ Under unfavorable conditions it thus seems likely that an AV fistula could improve patency of autogenous venous reconstruction.

Previous experiments with synthetic reconstruction have, in most instances, supported the use of an AV fistula.* Heydorn et al.¹⁷ however, noted no effect of an AV fistula on patency of ePTFE grafts placed in the superior vena cava. This study is compromised by a small number of observations, which precluded statistical evaluation. The graft failures presented were claimed to be due to anastomotic stricture, which has not been shown to be affected by the addition of an AV fistula. In a few previous studies,^{11,38,40} astonishing success rates have been achieved with ePTFE grafts without the use of an AV fistula. The common denominator of these experiments is that the graft segment used has been too short to allow clinical applicability. We used 12 cm long grafts placed in a position usually used in clinical practice, thus permitting more certain conclusions.

Although the occlusion rate of ePTFE grafts decreased drastically with an AV fistula, we noted some instances of pulmonary embolism from the occluded grafts if an AV fistula had been used. We have found no reports of clinical correlation to this experimental finding.

Although today it is commonly accepted that the AV fistula acts mainly by increasing blood flow,^{8,25,47} its effect on venous pressure has been suggested to

*References 1, 13, 17, 20, 23, 27, 30, 36, 47.

decrease the collapsibility of the graft walls.¹ Since the intravenous pressure is normalized within a few centimeters proximal to the AV fistula,^{25,47} this effect of the AV fistula is not likely. Various means of increasing graft wall rigidity have been tried⁴⁸ and have rendered a suggested positive effect. No study, including ours, has been conclusive. Perhaps the benefit of graft-wall support is marginal and a larger series and longer follow-up are necessary to provide sufficient information.

We thus conclude that the thrombogenicity of the graft material and the low velocity of blood flow explain the high failure rate of synthetic prostheses placed in the venous system. Further refinement of graft materials as well as drug administration or incorporation seem to be necessary to decrease graft thrombogenicity. The increased velocity of blood flow provided by an AV fistula is mandatory to achieve success with vascular prostheses placed in the venous system. The need for an AV fistula with reconstruction with autogenous vein grafts is not clearly defined but is probably indicated in unfavorable circumstances. Wall suspension does not seem to be of major importance for retaining graft patency.

The grafts used in this study were generously provided to us by W. L. Gore & Associates, Inc., Flagstaff, Ariz. We appreciate the technical assistance of Mr. O. Arlan Hildesstad, Mr. Michael L. Kapinos, Mrs. Kathy J. Topham, and Mr. Julijis Zarins.

*References 9, 10, 25, 26, 44.

REFERENCES

1. Eryant MF, Lazenby WD, Howard JM: Experimental replacement of short segments of veins. *Arch Surg* 76:289-93, 1958
2. Calvert MH, Gough MH: The effect of anti-thrombotic drugs on prosthetic grafts in the canine inferior vena cava. *Br J Surg* 63:910-3, 1976
3. Cockett FB, Lea Thomas M, Negus D: Iliac vein compression—Its relation to iliofemoral thrombosis and the post-thrombotic syndrome. *Br Med J* 2:14-9, 1967
4. Collins HA, Burrus G, DeBakey ME: Experimental evaluation of grafts in the canine inferior vena cava. *Am J Surg* 99:40-3, 1960
5. Dale WA: Reconstructive venous surgery. *Arch Surg* 114:1312-8, 1979
6. Dale WA, Scott HW: Grafts of the venous system. *SURGERY* 53:52-73, 1963
7. Dewanjee MK, Rao SA, Didisheim P: Indium-111 tropolone, a new high-affinity platelet label: Preparation and evaluation of labeling parameters. *J Nucl Med* 22:981-7, 1981
8. Dost K: Druck und Flussgeschwindigkeit in der Vene bei plastischem Venenersatz. *Angiologia* 5:271-9, 1968
9. Enerson DM, Galante N: The use of externally-supported aortic homografts in the superior vena cava. *Surg Forum* 8:450-4, 1957
10. Fiore AC, Brown JW, Cromartie RS, Ofstein LC, Peigh PS, Sears NS, Deschner WP, King H: Prosthetic replacement for the thoracic vena cava. *J Thorac Cardiovasc Surg* 84:560-8, 1982
11. Florian A, Cohn LH, Dammin GJ, Collins JJ: Small vessel replacement with Gore-Tex (polytetrafluoroethylene). *Arch Surg* 111:267-70, 1976
12. Fraker PJ, Speck JC: Protein and cell membrane iodinations with a sparingly soluble chloramide, 1,3,4,6-tetrachloro-3,6-diphenylglycoluril. *Biochem Biophys Res Commun* 80:849-57, 1978
13. Glowiczki P, Hollier LH, Dewanjee MK, Trastek VF, Hoffman EA, Kaye MP: Experimental replacement of the inferior vena cava: Factors affecting patency. *SURGERY* 95:657, 1984
14. Gruss JD, Bartels D, Kawai S, Karademos C, Tsafandakis E: Application of plastic material in the PALMA operation. *Angiology* 1:51-7, 1979
15. Haimovici H, Hoffer PW, Zincola N, Steinman C: An experimental and clinical evaluation of grafts in the venous system. *Surg Gynecol Obstet* 131:1173-86, 1970
16. Hasegawa T, Matsumoto H, Yamamoto M, Fuse K, Mizuno A, Saigusa M: Prosthetic replacement of superior vena cava: Anti-platelet-adhesive drug influence. *Arch Surg* 106:848-50, 1973
17. Heydorn WH, Zajchuk P, Miller J, Schuchmann GF: Gore-Tex grafts for replacement of the superior vena cava. *Ann Thorac Surg* 23:539-44, 1977
18. Hiratzka LF, Wright CB: Experimental and clinical results of grafts in the venous system: A current review. *J Surg Res* 25:542-61, 1978
19. Hobson RW, Howard EW, Wright CB, Collins GJ, Rich NM: Hemodynamics of canine femoral venous ligation: Significance in combined arterial and venous injuries. *SURGERY* 74:824-9, 1973
20. Holt MH, Lewis FJ: Experimental grafts of the superior vena cava with temporary arteriovenous shunts. *J Thorac Cardiovasc Surg* 49:818-23, 1965
21. Hughes CW: Arterial repair during the Korean War. *Ann Surg* 147:555-61, 1958
22. Husni EA: Venous reconstruction in postphlebitic disease. *Circulation* 43(suppl 1):147-50, 1971
23. Johnson V, Eiseaman B: Evaluation of arteriovenous shunt to maintain patency of venous autograft. *Am J Surg* 118:915-20, 1969
24. Kunlin J: Le rétablissement de la circulation veineuse par greffe en cas d'obliteration traumatique ou thrombophlébique. *Mem Acad Chir* 79:109-110, 1953
25. Kunlin J, Kunlin A: Experimental venous surgery. In May R, editor: *Surgery of the veins of the leg and pelvis*. Stuttgart, 1979, Georg Thieme Verlag, pp 37-75
26. Leshnower AC, Shumacker HB, Shariatizadeh AN: Experimental studies with synthetic venous bypass grafts, including a new experimental model. *Am J Surg* 128:392-7, 1974
27. Levin PM, Rich NM, Hutton JE, Barker WF, Zeller JA: Role of arteriovenous shunts in venous reconstruction. *Am J Surg* 122:183-91, 1971
28. Lovaas ME, Glowiczki P, Dewanjee MK, Hollier LH, Kaye MP: Inferior vena cava replacement: The role of antiplatelet therapy. *J Surg Res* 35:234-42, 1983
29. Madras PN, Johnson WR, Ward CA: Enhancement of throm-

- bus formation by vascular prostheses. *Can J Surg* 23:544-6, 1980
30. Mitsuoka H, Howard JM: Experimental grafting of the inferior vena cava. *J Cardiovasc Surg* 9:190-4, 1968
 31. Najjar FB, Gott VL: The use of small-diameter Dacron grafts with wall-bonded heparin for venous and arterial replacement: Canine studies and preliminary clinical experience. *SURGERY* 68:1053-63, 1970
 32. Noishiki Y, Nagaoka S, Kikuchi T, Mori Y: Application of porous heparinized polymer to vascular graft. *Trans Am Soc Artif Intern Organs* 27:213-8, 1981
 33. Palma EC, Esperon R: Vein transplants and grafts in the surgical treatment of the postphlebotic syndrome. *J Cardiovasc Surg* 1:94-107, 1960
 34. Plate G, Broomé A, Einarsson E, Eklöf B, Ohlin P: Results of early reconstruction in acute iliac vein obstruction using PTFE grafts. *Acta Chir Scand [Suppl]* 506:36, 1981 (abstr)
 35. Sawyer PN, Stanczewski B, Lucas TR, Srinivasan S, Ramasamy N, Kirschenbaum D: Physical chemistry of the vascular interface. In Sawyer PN, Kaplitt MJ, editors: *Vascular grafts*. New York, Appleton-Century-Crofts, pp 53-75
 36. Scheinin TM: Temporary arteriovenous fistula in experimental replacement of the inferior vena cava. *Acta Chir Scand [Suppl]* 357:286-90, 1966
 37. Scherck JP, Kerstein MD, Stansel HC: The current status of vena caval replacement. *SURGERY* 76:209-33, 1974
 38. Smith DE, Hammon J, Anane-Sefah J, Richardson RS, Trimble C: Segmental venous replacement. *J Thorac Cardiovasc Surg* 69:589-98, 1975
 39. Snyder MA, Adams JT, Schwartz SI: Hemodynamics of phlegmasia cerulea dolens. *Surg Gynecol Obstet* 125:342-6, 1967
 40. Soyer T, Lempien M, Cooper P, Norton L, Eiseman B: A new venous prosthesis. *SURGERY* 72:864-72, 1972
 41. Stallworth JM, Bradham GB, Kletke RR, Price RG: Phlegmasia cerulea dolens. *Ann Surg* 161:802-11, 1965
 42. Sullivan WG, Thornton FH, Baker LH, LaPlante ES, Cohen A: Early influence of popliteal vein repair in the treatment of popliteal vessel injuries. *Am J Surg* 122:528-31, 1971
 43. Takamatsu I: Absorption and desorption of heparin and persantin in expanded polytetrafluoroethylene tubes. Presented at the Eighth Annual Meeting of the Society of Biomaterials, Anaheim, Calif., April 24-27, 1982
 44. Todd RS, Sive EB, DeJode LR, Danese C, Howard JM: Replacement of segments of the venous system. *Arch Surg* 86:998-1002, 1963
 45. Vollmar J, Loeprich H, Hutschenreiter S: Rekonstruktive Eingriffe am Venensystem. *Chirurg* 49:296-302, 1978
 46. Wilson SE, Jabour A, Stone RT, Stanley TM: Patency of biologic and prosthetic inferior vena cava grafts with distal limb fistula. *Arch Surg* 113:1174-9, 1978
 47. Yamaguchi A, Eguchi S, Iwasaki T, Asano K: The influence of arteriovenous fistulae on the patency of synthetic inferior vena caval grafts. *J Cardiovasc Surg* 9:99-103, 1968

Endothelial seeding of venous prostheses

G. Plate, M.D., L. H. Hollier, M.D., R. J. Fowl, M.D., J. R. Sande, B.A., and
M. P. Kaye, M.D., Rochester, Minn.

To evaluate the potential benefit of endothelial seeding of venous prostheses, 20 dogs were subjected to ilioacaval reconstruction with expanded polytetrafluoroethylene grafts protected by an arteriovenous fistula. Grafts seeded with enzymatically derived endothelial cells were compared with control grafts that were sham seeded with culture medium and blood. Five seeded and seven sham-seeded grafts remained patent and were perfusion fixed in situ 4 to 6 weeks after operation. Specimens were examined by light, scanning, and transmission electron microscopy. No statistical difference in early patency was noted. The mean thrombus-free surface area was 80% in the seeded and 71% in the sham-seeded group. Light microscopy of these areas revealed a monocellular layer lining the lumen in all grafts. Scanning electron microscopy demonstrated a thin cellular lining covering 50% to 100% of the specimens' surface area in four of the five seeded and five of seven sham-seeded grafts. Transmission electron microscopy revealed these cells to exhibit characteristics typical of endothelial cells. The subcellular layer was equally thin in both groups. Early patency rates were not benefited by endothelial seeding of grafts placed in the venous system. Seeding of grafts with enzymatically derived endothelial cells provides a good endothelial cover with a thin subendothelial layer but not to a greater extent than does sham seeding of the venous prostheses.

From the Department of Surgery, Section of Vascular, Thoracic, and Cardiac Surgery, Mayo Clinic and Mayo Foundation, Rochester, Minn.

IN CASES OF POSTTHROMBOTIC occlusion, trauma, or tumor involvement of the major veins, autogenous vein grafts of adequate diameter are frequently not available for reconstruction. Vascular prosthetic grafts, although readily available, are fraught with a high incidence of both early and late occlusion when implanted in the venous system.^{4,12,16,17,19} Thrombogenicity of graft material and low flow in the venous system have usually been cited as common causes of graft failure.^{4,12,16,17} Attempts to increase flow by creation of a distal arteriovenous fistula have been shown to improve early patency,¹⁷ but late failure is frequent after closure of the arteriovenous fistula.¹⁹ More recently, endothelial seeding of prosthetic grafts has been shown to lessen the thrombogenicity of the blood-graft interface in the arterial system.²² To our knowledge, endothelial seeding has not been used in the venous system, where the

need for a nonthrombogenic graft surface seems more important than in the arterial system.

The present study was designed to evaluate the efficacy of endothelial seeding of venous prostheses and its effect on early patency.

MATERIAL AND METHODS

Twenty female mongrel dogs weighing 17 to 28 kg (mean 21 kg) were subjected to ilioacaval venous reconstruction. Each animal was anesthetized with intravenous pentobarbital sodium, intubated, and prepared in a sterile fashion and received a single preoperative dose of gentamicin sulfate (80 mg administered intravenously) and penicillin G benzathine (1.2 million U administered intramuscularly). The abdomen was entered through the midline and the left iliac vein and infrarenal vena cava were dissected free. Immediate endothelial seeding with enzymatically derived endothelial cells, as described by Graham et al.,¹⁰ was performed in 10 dogs. Twelve centimeters of the external jugular vein was harvested and everted on a 5 mm diameter stainless steel rod. This was suspended in iced calcium- and magnesium-free Hanks' balanced salt solution (Grand Island Biological Company, Grand Island, N.Y.) and

Presented at the Eighth Annual Meeting of the Southern Association for Vascular Surgery, St. Thomas, Virgin Islands, Jan. 18-21, 1984.

Supported in part by the Rappaport Clinician Investigation Fellowship Program.

Reprint requests: L. H. Hollier, M.D., Section of Vascular Surgery, Mayo Clinic, Rochester, MN 55905.

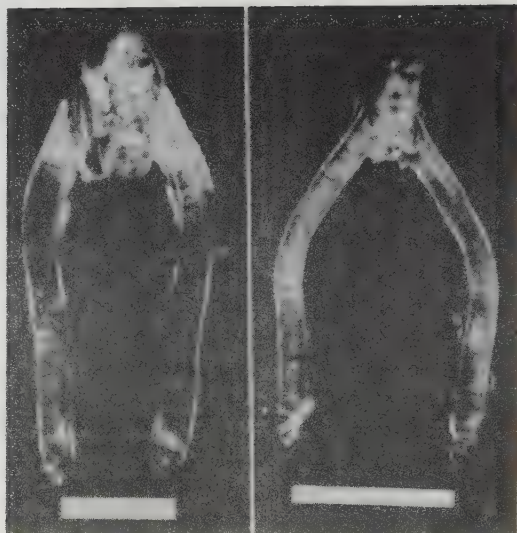


Fig. 1. One cPTFE graft seeded with endothelial cells (*left*) and one sham-seeded graft (*right*) stained with Evans blue and harvested 4 weeks after implantation in the ilio caval position in dogs.

Table I. Analysis of reendothelialization

Method	Endothelial-seeded grafts (n = 5)	Sham-seeded grafts (n = 7)
Gross examination (thrombus-free surface area)	80% $\pm$ 24%	71% $\pm$ 26%
Light microscopy (monocellular cover)	all	all
Scanning electron microscopy (50%-100% of surface covered)	4	5
Transmission electron microscopy (identified endothelium)	4	5

spun for 3 minutes at 200 to 300 rpm to remove residual blood. The vein was then incubated in 0.1% trypsin in calcium- and magnesium-free Hanks' solution with 0.125% EDTA at pH 8.0 for 10 minutes at 37° C. This was followed by immersion in 0.5%

collagenase (type 1, Worthington Biochemical Corp., Freehold, N.J.) in Hanks' solution with calcium and magnesium at pH 7.3 for an additional 10 minutes at 37° C. The vein was then spun in fresh culture medium (Medium 199, Grand Island Biological Co.) for 2 minutes at 200 to 300 rpm. The efficacy of cell harvest was checked by scanning electron microscopy of the donor vein. The tubes containing collagenase and culture medium were centrifuged for 3 minutes at 150 $\times$ g, resulting in bottom pellets with clusters of endothelial cells verified at light microscopy. The pellets were resuspended in 2 to 3 ml of fresh culture medium and mixed with 2 to 3 ml of nonheparinized blood obtained by puncture of the vena cava. This was infused and allowed to coagulate in a reinforced expanded polytetrafluoroethylene (ePTFE) graft (Gore-Tex, W.L. Gore & Associates, Inc.; external ring supported, 30 μ pore size, 8 mm inner diameter). Additionally, 10 control ePTFE grafts were sham seeded with nonheparinized blood mixed with culture medium but without endothelial cells. The grafts were finally flushed with 15 ml of heparinized blood and wrapped in a moist gauze.

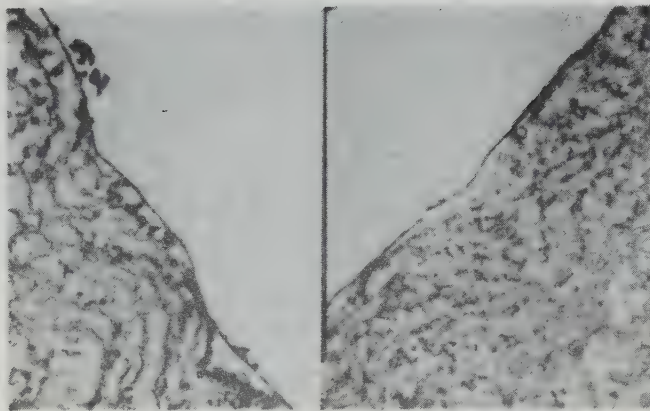


Fig. 2. Light photomicrographs of ePTFE graft seeded with endothelial cells (*left*) and sham-seeded graft (*right*) harvested 4 weeks after implantation in the ilio caval position in dogs. (Original magnification $\times 100$ and $\times 250$.)

After systemic heparinization (300 U/kg), the left iliac vein was transected and ligated. A 10 cm long graft segment was implanted between the left external iliac vein (end-to-end) and the inferior vena cava (end-to-side) with continuous 6-0 Prolene sutures. A distal arteriovenous fistula was constructed before reinstitution of blood flow. This fistula was created through a separate left groin incision, where an 8 mm long side-to-side anastomosis was performed between the superficial femoral artery and vein with 7-0 Prolene sutures. Flow was reinstituted and the wounds were closed in anatomic layers.

The grafts were harvested 4 to 6 weeks after operation. Two hours after an intravenous injection of 2 ml/kg of a 0.5% solution of Evans blue, the dogs were anesthetized with pentobarbital sodium, and the grafts were dissected free. The dogs were heparinized and the grafts were cannulated and perfused with normal saline solution and then perfusion fixed *in situ* for 30 minutes with buffered glutaraldehyde and formalin (Trump's solution) at a pressure of 10 cm of water. After removal of the grafts, the fixation was continued for another 24 hours in the refrigerator.

The grafts were opened longitudinally, grossly examined, and photographed. The patency rate and mean thrombus-free surface area in the two groups were calculated. Microscopic evaluation of endothelialization was performed on specimens obtained from

thrombus-free surface areas in the center of patent grafts at a distance of at least 3 cm from the anastomoses. Light microscopy specimens were stained with standard hematoxylin-eosin stain and selected specimens were also stained with Jones' methenamine silver to verify the presence of a basement membrane. In addition, sections from all grafts were processed with the standard methods for scanning and transmission electron microscopy. The endothelial coverage of each scanning electron microscopy specimen was quantified and the group's mean coverage calculated. Transmission electron microscopy was used for identification of cell types lining the luminal surface and for calculation of neointimal thickness.

Statistical evaluation was performed with the one-tailed Student *t* test for quantitative data and the χ^2 analysis for qualitative data.

RESULTS

One dog in each group died within the first 2 weeks and autopsy examination revealed no surgically related cause of death. The grafts were found to be patent with insignificant mural thrombus formation. Four of the seeded grafts and two sham-seeded grafts were found to be occluded at death. The early patency was thus six of 10 in the seeded and eight of 10 in the sham-seeded group ($p > 0.3$).

Five seeded and seven sham-seeded grafts were thus

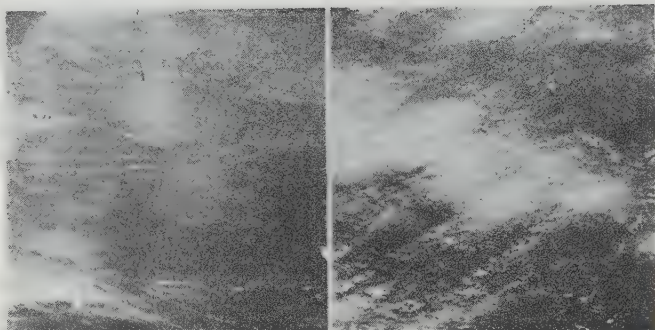


Fig. 3. Scanning electron photomicrographs of ePTFE graft seeded with endothelial cells (left) and sham-seeded graft (right) harvested 4 weeks after implantation in the ilio caval position in dogs. (Original magnification $\times 1700$).

available for analysis of reendothelialization (Table I). Gross examination (Fig. 1) demonstrated a total absence of mural thrombus formation in two seeded and one sham-seeded graft. When present, thrombi were located primarily in the cranial third of the grafts. The mean thrombus-free surface area was $80\% \pm 24\%$ in the seeded group and $71\% \pm 26\%$ in the sham-seeded group ($p > 0.25$).

Light microscopy (Fig. 2) revealed that the luminal surface was composed of a monolayer of flat cells in all seeded and sham-seeded grafts. The presence of basement membrane was confirmed on selected specimens from both groups stained with Jones' methenamine silver. Microscopic mural thrombi were partly covered with a similar monolayer of cells.

Scanning electron microscopy (Fig. 3) demonstrated, in four seeded and five sham-seeded grafts, a thin luminal layer, usually revealing the undulating structure of the graft material beneath. This layer covered 50% to 100% of the specimens' surface area and was composed of flat polygonal cells elongated in the direction of blood flow and with a continuous cell border. Very few platelets were seen in the areas covered with these endothelial-like cells. One seeded and two sham-seeded grafts were covered by an irregular carpet of fresh cells and old platelets and other blood cells.

Transmission electron microscopy (Fig. 4) demonstrated that the cells lining the luminal surface of four seeded and five sham-seeded grafts exhibited several characteristics typical of endothelial cells. The cells were flat with bipolar cell processes resting on a

basement membrane-like surface that was only 1 to 4 μ thick in both groups. Numerous pinocytotic vesicles were found within the cytoplasm at both the outer and inner surfaces. Interdigitating cell borders with tight junctions were constantly noted, but we found no Weibel-Palade bodies. A rough endoplasmic reticulum was never observed in the cytoplasm of these cells.

DISCUSSION

The etiology of venous prosthetic occlusion is thought to be caused by the low flow rate combined with the thrombogenicity of the graft material.^{4, 12, 16, 17} The construction of a flow-increasing arteriovenous fistula has proved to increase early patency in experimental and clinical cases.^{12, 17} When used for a long term, such fistulas may have deleterious effects on the heart and can therefore be used only to protect the grafts from early occlusion.¹⁷ Although enhancing early patency, experimental experience with venous prostheses demonstrates that deposition of thrombus material on the prosthetic surface continues after fistula closure.⁸ Limited clinical experience with an arteriovenous fistula created at the time of venous reconstruction confirms the high incidence of occlusion after fistula closure.¹⁹

It is thus obvious that other measures are needed to decrease graft thrombogenicity in an attempt to ensure continued patency of venous prostheses. Long-term anticoagulation and antiplatelet treatment have been used for this purpose with variable results.^{4, 8, 12, 13, 17}

The technique of endothelial seeding has been introduced recently for arterial reconstruction in an

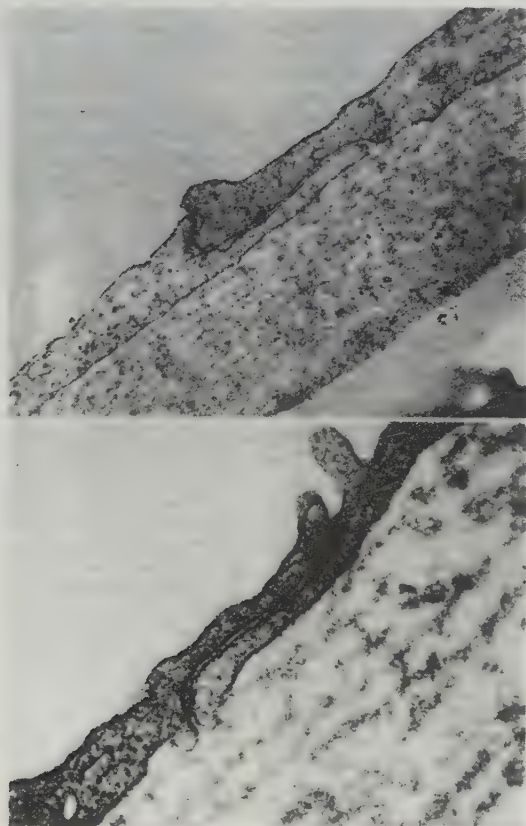


Fig. 4. Transmission electron photomicrographs of ePTFE graft seeded with endothelial cells (*top*) and sham-seeded graft (*bottom*) harvested 4 weeks after implantation in the ilio caval position in dogs. (Original magnification $\times 43000$ and $\times 70000$.)

attempt to create a nonthrombogenic blood-graft interface on vascular prostheses.^{11,15} Endothelial cells derived from autogenous veins by mechanical^{14,15} or enzymatic^{2,3,9-11,21,25} methods have been seeded into Dacron or ePTFE grafts before implantation in animals and have resulted in the formation of a 60% to 90% endothelial luminal lining after 2 to 6 weeks. A normalization in platelet survival accompanying endothelial seeding has also been demonstrated by Sharfkin et al.²²

Since vascular grafts implanted in veins have a great tendency to occlude,^{4,12,16,17,19} the need for a nonthrombogenic vascular conduit suitable for the venous system is apparent. This study was performed to analyze the feasibility of endothelial seeding of venous prostheses and its potential benefit on patency.

We did not find that endothelial seeding of ePTFE grafts implanted in the ilio caval position in dogs improved the early patency rate. Forty percent of the seeded grafts occluded within 1 month, which was not

statistically different from the 30% early occlusion rate achieved in a previous study without seeding in our laboratory (unpublished data) or from the sham-seeded grafts in the current study. Only two of the five patent grafts harvested 4 to 6 weeks after endothelial seeding and implantation had a luminal surface completely free of mural thrombus. Light microscopy of the thrombus-free area demonstrated a monocellular surface lining in all grafts. A thin cellular coverage of 50% to 100% was found with scanning electron microscopy in four grafts. Transmission electron microscopy provided significant evidence that these cells were true endothelial cells. It can therefore be concluded that endothelial seeding of venous prostheses is feasible in the dog model. However, this does not seem to prevent early occlusion and mural thrombus formation in venous prostheses. Our data agree with previous findings that a sufficient endothelial cover is not obtained within the first weeks after endothelial seeding.³ Other means are therefore needed to protect venous grafts from early occlusion. If the endothelial cover obtained later improves, long-term patency of venous prostheses needs to be evaluated.

Of great significance in this study was the fact that control grafts that had been sham seeded with nonheparinized blood and culture medium achieved an endothelial cover on the luminal surface that was not different in extent or character from the seeded grafts. The grafts appeared similar on gross examination and a monocellular surface lining was found with light microscopy in the center of all grafts in both groups. Scanning electron microscopy demonstrated endothelial-like cells covering 50% to 100% of the luminal surface in four seeded and five sham-seeded grafts. Transmission electron microscopy confirmed that these cells exhibited several important characteristics of endothelial cells.

Thus our findings of early reendothelialization of control grafts conflict with previous clinical and experimental experience. Sauvage et al.²⁰ and others^{18, 21} have reported that vascular prostheses, including ePTFE grafts implanted in the arterial system of humans, essentially never obtained an internal endothelial lining. Previous reports of ePTFE grafts implanted in the canine venous system have also demonstrated a lack of endothelial coverage in the center of the grafts.^{8, 24} Although the recent report by Wolf et al.²⁷ supports our findings that venous prostheses could be reendothelialized, their study used only very short graft segments that were harvested much later. Our results are also in conflict with the reported experience with endothelial seeding by Grahm et al.⁹ These authors performed sham seeding in a similar way as in the present study

but did not find endothelium in the graft center after 2 to 4 weeks.

To seek resolution of these conflicting reports, one must carefully examine the criteria for identifying true endothelium. Gross examination of grafts is often misleading, even after staining with Evans blue.⁷ Light microscopy can demonstrate a monocellular surface lining with characteristics of endothelium and presence of a basement membrane but is not considered sufficient as proof of reendothelialization.⁷ Scanning electron microscopy provides information of the extent of cellular cover and can almost certainly identify endothelium.⁷ Confluent cell layers with nonoverlapping intercellular junctions not covered with platelets are characteristic features that were all identified on the four seeded and five sham-seeded grafts in our study. Findings on transmission electron microscopy of flat bipolar cells with pinocytotic vesicles at both cell surfaces and interdigitating cell borders with tight junctions are claimed to characterize true endothelium.^{5, 6} All of these features were present in the cellular lining noted in our study. Weibel-Palade bodies are specific markers⁵⁻⁷ that were not identified in our specimens. These bodies are rare and their absence does not disprove the endothelial identity.⁷ Immunohistologic staining has been used for positive identification of endothelium, but this method has other limitations⁷ and would therefore probably not have increased the reliability of our results. It can thus be stated that the cells that were identified in the center of our seeded as well as sham-seeded grafts, with the criteria available today, must be considered as true endothelial cells.

How has this reendothelialization of the graft center occurred? Vollmar²⁶ has considered three possible sources for endothelial recovery: (1) transformation of fibrocytes after invasion of the graft wall, (2) ingrowth of endothelium from the anastomoses, and (3) transformation of blood elements. The first possibility, transformation of invading fibrocytes, is unlikely to have occurred in our grafts since ingrowth through the low porous ePTFE material is unlikely or at least delayed.²⁶ Transmission electron microscopy of the cells lining our grafts did not demonstrate any rough endoplasmic reticulum, which is a characteristic feature of fibrocytes.⁵ The second possible mechanism of reendothelialization, ingrowth from the anastomoses, varies considerably among species. In this aspect, however, dogs are similar to humans.²⁰ According to published data,^{9, 20} the anastomotic ingrowth in canine arterial grafts does not reach more than 10 mm at 4 weeks after implantation. Our grafts were 10 cm long and the specimens examined were obtained at a distance of at least 3 cm from the anastomoses. Hence

anastomotic ingrowth is an unlikely explanation for reendothelialization of the center of the graft. The third theory, that the new endothelium is derived from transformed blood elements, is still possible.

The endothelial coverage obtained in the seeded grafts could very well have resulted from the cells harvested from the jugular vein. However, the seeding material in the sham-seeded group did not contain any harvested cells. The question then arises if the nonheparinized blood and culture medium used for sham seeding of these grafts has played an important role in the reendothelialization. The difference in endothelial recovery after sham seeding in our study and the previous study by Graham et al.⁹ cannot be explained at the present time. We found that 50% to 100% of the thrombus-free surface area was covered with endothelial cells in five of the seven sham-seeded grafts 4 to 6 weeks after implantation, whereas Graham et al. found only one island of endothelium in one of five sham-seeded grafts harvested 2 to 4 weeks after implantation. The graft material used was identical and the technique of sham seeding similar, although we used a higher concentration of culture medium. In both studies the number of observations was not large. A significant difference between the two studies is that our study was performed in the venous system, whereas the grafts used by Graham et al. were placed in the arterial system. The influence of an arteriovenous fistula on endothelial covering is not known. The grafts used by Graham et al. were harvested earlier than our grafts and these authors did not indicate whether the grafts were fixed in situ. No clear-cut reason for the difference in results can be offered at this time.

Although no definitive conclusion can be drawn from these experiments regarding endothelial growth, we can conclude that seeding does not enhance patency of grafts in the venous system in dogs. Our data also permit us to ask the question, "Will the proper culture media and surface conditions permit early, complete endothelialization of vascular grafts?"

REFERENCES

- Berger K, Sauvage LR, Rao AM, et al: Healing of arterial prostheses in man. *Ann Surg* 175:118-27, 1972
- Burkel WE, Ford JW, Vinter DW, et al: Endothelial seeding of enzymatically derived and cultured cells on prosthetic grafts. In Stanley JC, editor: *Biologic and synthetic vascular prostheses*. New York, 1982, Grune & Stratton, pp 631-51
- Burkel WE, Vinter DW, Ford JW, et al: Sequential studies of healing in endothelial seeded vascular prostheses: Histologic and ultrastructure characteristics of graft incorporation. *J Surg Res* 30:305-24, 1981
- Dale WA, Scott HW Jr: Grafts of the venous system. *Surgery* 53:52-73, 1963
- Erlandson RA: *Diagnostic transmission electron microscopy of human tumors*. New York, 1981, Masson Publishing USA Inc
- Ferrans VJ, Thiedemann KU: Ultrastructure of the normal heart. In Silver MD, editor: *Cardiovascular pathology*, vol 1. New York, 1983, Churchill Livingstone Inc, pp 31-86
- Ford JW: Methods for macroscopic and microscopic analysis of experimentally implanted prosthetic vascular grafts. In Stanley JC, editor: *Biologic and synthetic vascular prostheses*. New York, 1982, Grune & Stratton, pp 257-76
- Głowiczki P, Hollier LH, Dewanjee MK, Trastek VF, Hoffman EA, Kaye MP: Experimental replacement of the inferior vena cava: Factors affecting patency. *Surgery* 95:657-66, 1984
- Graham LM, Burkel WE, Ford JW, et al: Expanded polytetrafluoroethylene vascular prostheses seeded with enzymatically derived and cultured canine endothelial cells. *Surgery* 91:550-9, 1982
- Graham LM, Burkel WE, Ford JW, et al: Immediate seeding of enzymatically derived endothelium in Dacron vascular grafts. *Arch Surg* 115:1289-94, 1980
- Graham LM, Vinter DW, Ford JW, et al: Endothelial cell seeding of prosthetic vascular grafts. *Arch Surg* 115:929-33, 1980
- Haimovici H, Hoffer PW, Zinicola N, Steinman C: An experimental and clinical evaluation of grafts in the venous system. *Surg Gynecol Obstet* 131:1173-86, 1970
- Hasegawa T, Matsumoto H, Yamamoto M, et al: Posthectic replacement of superior vena cava. Anti-platelet-adhesive drug influence. *Arch Surg* 106:848-50, 1973
- Herring MB, Dille R, Jersild RA, et al: Seeding arterial prostheses with vascular endothelium. The nature of the lining. *Ann Surg* 190:84-90, 1979
- Herring M, Gardner A, Glover J: A single-staged technique for seeding vascular grafts with autogenous endothelium. *Surgery* 84:498-504, 1978
- Hiratzka LF, Wright CB: Experimental and clinical results of grafts in the venous system. A current review. *J Surg Res* 25:542-61, 1978
- Kunlin J, Kunlin A: Experimental venous surgery. In May R, editor: *Surgery of the veins of the leg and pelvis*. Stuttgart, 1979, Georg Thieme Verlag, pp 37-75
- Mohring K, Asbach HW, Busch W, et al: Clinical implications of pathomorphological findings in vascular prostheses. In Hawkins R, editor: *Dialysis, transplantation, nephrology*. London, 1978, Pitman Books Ltd, pp 582-3
- Plate G, Broome A, Einarsson E, et al: Results of early reconstruction in acute iliac vein obstruction using PTFE grafts (abstr). *Acta Chir Scand [Suppl]* 506:36, 1981
- Sauvage LR, Berger KE, Wood SJ, et al: Interspecies healing of porous arterial prostheses. Observations 1960 to 1974. *Arch Surg* 109:698-705, 1974
- Sharefkin JB, Latker CH, D'Amore PA, et al: Seeding of Dacron vascular prostheses with endothelium of aortic origin. *J Surg Res* 34:33-43, 1983
- Sharefkin JB, Latker C, Smith M, et al: Early normalization of platelet survival by endothelial seeding of Dacron arterial prostheses in dogs. *Surgery* 92:385-93, 1982
- Sottiturai VS, Yao JST, Flinn WR, Batson RC: Intimal hyperplasia and neointima: An ultrastructural analysis of thrombosed grafts in humans. *Surgery* 93:809-17, 1983
- Soyer T, Lempienen M, Cooper P, Norton L, Eisman B: A new venous prosthesis. *Surgery* 72:864-72, 1972
- Stanley JC, Burkel WE, Ford JW, et al: Enhanced patency of

small-diameter, externally supported Dacron iliofemoral grafts seeded with endothelial cells. *SURGERY* 82:994-1005, 1982

26. Vollmar J: Vascular replacement. In Vollmar J, editor: *Reconstructive surgery of the arteries*. Stuttgart, 1980, Georg Thieme Verlag, pp 33-57

27. Wolf H, Ayisi K, Docin N, et al: Demonstration of neointima in PTFE prostheses after venous replacement in dogs. Presented at the thirteenth World Congress of the International Union of Angiology, Rochester, Minn., Sept. 11-16, 1983

PRINTING
ILLUSTRATION DEPARTMENT
DEPARTMENT OF SURGERY
UNIVERSITY OF LUND
1985.